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INFECTIOUS LYMPHOCYTOSIS

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Lymphocytic reactions in childhood afford difficulties in interpretation because a predominance of lymphocytes and a greater lability of the blood-forming mechanism constitute normal features of this period. A marked increase in lymphocytes is a well known accompaniment of certain infections, such as pertussis, and of postinfectious states, while leukopenia with a relative increase in lymphocytes characterizes the blood reaction in typhoid fever and influenza. A lymphocytic increase may occur, however, in infants and children when a specific etiologic agent or a well defined clinical condition cannot be demonstrated.

Two types of conditions are encountered in young patients which are characterized by lymphocytosis and which are frequently confused with infectious mononucleosis, or even with leukemia. In one, transient, unexpected hyperleukocytosis with an absolute and a relative increase in lymphocytes occurs and is unassociated with recognizable symptoms or physical signs. The second type, which is more frequently encountered, follows infections of the upper respiratory tract, of varying severity. It is characterized by low grade fever, present for weeks or months, and associated symptoms frequently include anorexia, pallor, fatigability and abdominal pain, usually referred to the region of the umbilicus. In both conditions there is a preponderance of lymphocytes in the blood with a normal or a moderate elevation of the total cell count. The lymphocytes are essentially normal, with only a few of the cells exhibiting deviations of diagnostic importance.

It is the purpose of this paper to present cases illustrating the hematologic and the clinical features of these syndromes and to differentiate them from infectious mononucleosis and from lymphocytic leukemia. Their separation from infectious mononucleosis is of especial interest because the definition of the latter disease has recently been given wide latitude. A condition in which there are an unexplained lymphocytic response of the blood, with no increased titer of heterophile agglutinins,

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and equivocal symptoms and physical signs is often designated infectious mononucleosis because of the lack of any other appropriate hematologic classification. It is suggested that the terms "acute and chronic infectious lymphocytosis" may properly be applied to the conditions in the two groups of cases to be described.

NORMAL VALUES FOR BLOOD AND BONE MARROW

An analysis of the blood responses to be described in this paper necessitates a brief consideration of normal blood values. Young subjects, particularly infants, normally exhibit a wide range of individual variability in the number of white cells in the peripheral blood, and the hematopoietic system of young persons is more labile in responding to stimuli than that of adults. In addition, the successive growth and developmental periods are associated with concurrent changes in the hematologic formula. Despite these difficulties, it is possible to designate standards for comparative purposes. Such standards are especially important in evaluating lymphocytic elevations, since these cells, in contradistinction to other types, vary markedly in percentage and in absolute number, especially in the infant and the young child.

Total White Cell Count.—The enumeration of the total number of white cells and of the average numbers of the other cellular elements in the blood has been the subject of many reports. While absolute conformity is not realized, in general the reports agree that the average total leukocyte count drops from 11,000 per cubic millimeter at 3 months of age to between 8,000 and 10,000 at 1 year, to 8,000 at 10 years and to values slightly below this level during adolescence; eventually the number of cells declines to the adult level of 6,000 to 7,000.[1] The maximal values show a corresponding fall from 13,000 in the first year to 11,000 at 15 years of age.[2]

Absolute and Relative Lymphocyte Count.—For a valid assessment of lymphocytosis absolute values must be considered. Relative lymphocytosis, as indicated by a high percentage of lymphocytes when the total count is low or normal, may be equivalent to a normal absolute number

1. (*a*) Kato, K.: Leucocytes in Infancy and Childhood, J. Pediat. **7**:7 (July) 1935. (*b*) Benjamin, B., and Ward, S. M.: Leukocytic Response to Measles, Am. J. Dis. Child. **44**:921 (Nov.) 1932. (*c*) Wollstein, M.: Normal Blood in Infants and Children, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 2, p. 937. (*d*) Osgood, E. E.; Baker, R. L.; Brownlee, I. E.; Osgood, M. W.; Ellis, D. M., and Cohen, W.: Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates for Healthy Children: Standards for Children Eight to Fourteen Years of Age, Am. J. Dis. Child. **58**:282 (Aug.) 1939.

2. Kato.[1a] Benjamin and Ward.[1b]

of lymphocytes and a decrease in the total number of polymorphonuclear elements. Information concerning the granulocytes is important, since neutropenia indicates that the bone marrow has been injured by the causative agent. When the lymphocytes are numerically unaltered, however, involvement of the lymphatic structures is often manifested by the presence of abnormal lymphocytes.

During the first week of life the number of polymorphonuclear leukocytes exceeds that of lymphocytes; by the end of the first week the two types of cells are equal in number, after which the lymphocytes predominate for the remainder of infancy. From the third to the fifth year the numbers of these two types of cells are again approximately equal, and thereafter the granulocytes slowly increase to the adult value of about 60 per cent and the lymphocytes decrease to 25 or 30 per cent, these levels being usually attained at about 12 years of age. Kato [1a] found that at the end of the first week of life and at 4 years of age the absolute and relative values for the granulocytes and the lymphocytes are identical, being 4,000, or 40 per cent, of each at the former and 4,000, or 50 per cent, at the latter age level.

Since the lymphocytic response appears to constitute an outstanding feature of the syndrome to be described, a knowledge of the normal maximal values at the different age periods is a prerequisite for valid interpretation of the lymphocytic response in the illustrative cases which follow. The maximal normal lymphocytic percentage is approximately 60 between 6 months and 2 years of age, 50 by the end of the sixth year, 45 by the eighth year and 40 subsequently to adult life. The maximal normal absolute number of lymphocytes drops progressively from approximately 7,000 at 1 to 2 years of age, to 6,000 at 3 to 4 years and finally to 5,000 at puberty.

The Granulocyte Count.—To establish the true nature of the composite blood picture the effect on the granulocytes must also be known. To gage a decrease in polymorphonuclear cells the absolute number of these cells should be compared with the normal minimal levels. Instead of designating lower levels, however, average values have been substituted, so as not to complicate this study by including two standards, a minimum and an average. An increase in polymorphonuclear leukocytes occurring in conjunction with lymphocytosis may be readily noted by comparison with the average values. A suppression of granulocytes, on the other hand, may also be detected by comparison of the absolute with the normal average number; an extreme decrease is readily discernible. The average values for the polymorphonuclear neutrophils are fairly constant during the greater part of infancy and childhood. Benjamin and Ward [1b] found that they range from 4,500 to 5,100 between 6 months of age and the adult period, with attainment of the higher values at the 5 to

8 year level. The average figures given by Kato [1a] for granulocytes, of which polymorphonuclear neutrophils constitute the greater part, range from 3,000, or 32.2 per cent, in the second month to 4,000, or 50 per cent, at 4 years and finally to 5,000, or 62.6 per cent, at 15 years of age.

Hemoglobin Content and Red Cell Count.—In addition to the effect on the white cells, alterations in the hemoglobin content and the number of red cells occur, and for this reason values for these elements have also been included in this report. During the first two years of life the hemoglobin content normally ranges from approximately 10 to 12.5 Gm. per hundred cubic centimeters of blood, with an average value of 11 Gm. Between 3 and 5 years of age it ranges from 12.5 to 13 Gm., and between 5 and 10 years from 13 to 13.5 Gm.; during puberty it rises gradually to the adult value of 14.5 Gm.[3] A count of 4,000,000 red cells per cubic millimeter of blood may be regarded as the lower limit of normal for the older infant and child.

Differential Count.—At least 300 white cells were counted to determine the differential percentages. Preliminary observation of larger fields with lower magnification was useful in deciding whether the smear was predominantly neutrophilic or lymphocytic. By this means, also, only those slides were used in which the distribution of the cells was uniform. The fixed smears were stained by Wright's method, and care was taken to guard against overstaining, since great importance is attached to the degree of basophilia of the cytoplasm and to the nuclear pattern.

Other Blood Values.—A number of other measurements were made in many cases. The volume of packed red cells per hundred cubic centimeters of blood was obtained by means of a hematocrit tube.[4] Measurement of the corpuscular volume constitutes an excellent comparative index of the mass of red cells, since this value includes their number, size and volume. Thirty-six per cent was considered the minimal normal value for the group of children under consideration.[5] In a few cases the sedimentation rate was determined, and with the microsedimentation method [4] employed the average normal value was 9 mm. at the end of an hour, with a range from 3 to 13 mm.

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3. Mugrage, E. R., and Andresen, M. I.: Values for Red Blood Cells of Average Infants and Children, Am. J. Dis. Child. **51**:775 (April) 1936. Faergeman, P.: Normal Values for Hemoglobin, Erythrocytes and Cell Volume Per Cent, and Corpuscular Constants Derived Thereof, in Children Aged Eight to Fourteen Years, Acta med. Scandinav. **95**:566, 1938.

4. Smith, C. H.: Method for Determining the Sedimentation Rate and Red Cell Volume in Infants and Children with the Use of Capillary Blood, Am. J. M. Sc. **192**:73 (July) 1936.

5. Smith, C. H.: Sedimentation Rate in Nutritional Anemia of Infants and Children, Am. J. Dis. Child. **56**:510 (Sept.) 1938.

The Paul-Bunnell test for sheep cell antibodies was performed to rule out infectious mononucleosis.

Bone Marrow Values.—Sternal puncture was performed in 3 cases. Information as to the normal range for the total nucleated cell count, the differential percentages for each type of cell, the variability in different age periods and the extent of individual fluctuations in bone marrow obtained by sternal aspiration is still limited. In a limited experience, counts of approximately 100,000 to 200,000 nucleated cells per cubic millimeter have been noted for normal children, with a higher upper limit for young infants. The following approximate percentage distribution of cells, based on available studies and personal experience, has been employed for comparative purposes: myeoblasts, 1 to 5 per cent; myelocytes (including promyelocytes), 10 to 25 per cent; nonsegmented polymorphonuclear neutrophils (including metamyelocytes) 15 to 30 per cent; segmented polymorphonuclear cells, 5 to 30 per cent; lymphocytes, 15 to 25 per cent, and total nucleated red cells, 15 to 30 per cent.

REPORT OF ILLUSTRATIVE CASES

Eleven cases will be briefly described, 2 of which are included in the group characterized by transitory hyperleukocytosis and a striking increase in lymphocytes and the remaining 9 in the group characterized by a less marked and more prolonged lymphocytosis.

GROUP 1: ACUTE INFECTIOUS LYMPHOCYTOSIS

CASE 1.—W. K., a boy 6¼ years of age, was admitted to the hospital on Jan. 13, 1940 for repair of an inguinal hernia. He had been admitted twice previously, the first time on May 12, 1935, because of lobar pneumonia and acute otitis media, and again on Nov. 1, 1938, because of loss of consciousness, the cause of which was never ascertained. During both hospitalizations there was moderate leukocytosis with a neutrophilic response.

On the present admission the patient appeared well and his temperature was normal. The heart and the lungs were normal. The cervical, axillary and inguinal nodes could be felt, but they were all small. The spleen and the liver were not palpable. The throat, which was normal on admission, was deeply injected nine days later. He remained afebrile, and there were no complaints.

Routine preoperative examination of the blood revealed an unsuspected leukocytosis, and operation was postponed. The course in the hospital was uneventful. The Paul-Bunnell tests, done on January 20 and February 28, gave negative results. The results of urinalyses and the reactions to tuberculin tests were always negative.

Examination of the sternal marrow on January 22 revealed 140,000 nucleated cells per cubic millimeter, and the megakaryocytes numbered 22 per cubic millimeter. The differential count was as follows: neutrophilic band forms, 16 per cent; segmented forms, 4 per cent; lymphocytes, 36 per cent; eosinophils, 1 per cent; myeloblasts, 1 per cent, neutrophilic myelocytes, 14 per cent; eosinophilic myelo-

TABLE 1.—*Hematologic Data for W. K. (Case 1)*

Age, Years	Date	Hemoglobin Content, Gm. per 100 Cc.	Red Cells, Millions per Cu. Mm.	Packed Red Cell, Volume per Cent	White Cells, per Cu. Mm.	Neutrophils				Lymphocytes		Monocytes, Percentage	Eosinophils, Percentage	Basophils, Percentage	Result of Paul-Bunnell Test
						Percentage	Number	Band	Segmented	Percentage	Number				
First Hospitalization, 5/12/35 to 6/30/35															
1½	5/12	10.0	3.89	..	19,500	83	16,185	42	41	14	2,730	3	..	..	.....
	5/16	....	....	..	11,000	82	9,020	39	43	16	1,760	2	..	..	.....
	6/16	....	....	..	13,000	85	11,050	33	52	23	2,990	1	1	..	.....
Second Hospitalization, 11/1/38 to 11/12/38															
5	11/1	13.0	4.36	..	16,700	80	13,360	12	68	20	3,340	..	..	..	.....
	11/4	....	....	..	8,200	57	4,674	20	37	40	3,280	0	3	..	.....
Third Hospitalization, 1/13/40 to 1/24/40															
6¼	1/13	14.0	4.00	..	42,900	13	5,577	0	13	78	33,462	2	5	1	.....
	1/14	....	....	..	44,300	15	6,645	5	10	79	34,997	1	3	1	.....
	1/15	15.0	4.70	..	40,200	27	10,854	17	10	60	24,120	0	10	1	.....
	1/17	12.5	4.50	..	39,000	20	7,800	6	14	72	28,080	2	4	1	.....
	1/20	....	....	..	.....	..	.....	..	..	..	.....	..	..	..	Negative
	1/22	11.0	4.41	38	24,900	20	4,980	3	17	72	17,928	3	5	..	.....
Outpatient Studies															
	2/27/40	12.0	4.31	38	15,500	63	9,765	6	57	32	4,960	5	..	..	.....
	2/28	....	....	..	.....	..	.....	..	..	..	.....	..	..	..	Negative
	5/28	13.0	5.13	41	7,000	34	2,380	2	32	60	4,200	4	2	..	.....
7¼	1/28/41	14.0	5.50	39	11,900	46	5,474	1	45	51	6,069	1	2	..	.....
	2/18	14.0	....	39	11,700	23	2,691	3	20	71	8,307	4	2	..	.....

cytes, 2 per cent; metamyelocytes, 10 per cent, and nucleated red cells, 16 per cent. The total count and the differential smear were essentially normal, the only unusual observation being an increase in the number of lymphocytes. The lymphocytes, however, were entirely normal.

Subsequent to discharge the patient was followed in the outpatient department. An abnormality noted consistently in his last examinations has been a slight to heavy postnasal discharge. The most recent counts (Jan. 28 and Feb. 18, 1941) have again shown moderate leukocytosis with a lymphocytic preponderance. The cultures of material from the nose and throat on May 12, 1935 and on Feb. 12, 1940 revealed practically the same bacterial flora, namely, hemolytic and nonhemolytic staphylococcus, Staphylococcus albus, Pneumococcus and diphtheroid organisms.

The blood counts made during the child's three hospitalizations are recorded in table 1.

CASE 2.—J. G., a boy 3½ years old, was admitted to the hospital on Nov. 14, 1940 so that an abnormal leukocytic reaction might be investigated. He had been hospitalized twice previously. The first time, on Dec. 8, 1938, he was admitted because of acute otitis media and rhinopharyngitis. The organisms found in the nose and throat included nonhemolytic streptococcus, Pneumococcus type 3 and Haemophilus influenzae. He was admitted again on Dec. 30, 1939 because of acute rhinopharyngitis, laryngitis and pansinusitis. The bacterial flora in the nose and throat corresponded to that observed during the previous hospitalization except that the influenza organism was not found. During these two hospitalizations there was moderate leukocytosis with a neutrophilic response.

The present illness dated back to Sept. 25, 1940, when the patient complained of pain in the back of the neck and in the head, for which he was admitted to another hospital. It was found there that he was afebrile, that his tonsils were hypertrophied and that the only other physical sign was the presence of small, shotty, posterior cervical and inguinal nodes. Examination of the blood revealed the abnormalities recorded in table 2. On the day of admission there were 98,000 white cells, 82 per cent of which were not identified at first but two days later were classified as lymphocytes. The child was discharged from this other institution on October 7 with a diagnosis of chronic lymphatic leukemia.

After his discharge he returned to the outpatient department of the New York Hospital. While he was under observation there he showed a slight, but persistent, elevation of temperature, which could be explained by an injected pharynx. The blood count on October 11 showed an elevation of the white cells to 26,000 per cubic millimeter, with 83 per cent lymphocytes. He was admitted to the hospital on November 14 for fuller study of the blood reaction.

Physical examination on admission revealed that he was well developed, and he did not appear ill. The head, eyes, ears and nose were normal. The tonsils were moderately hypertrophied and diffusely injected. The heart and lungs were normal, and the liver, spleen and kidneys could not be felt. The anterior cervical and axillary nodes were slightly enlarged. The roentgenograms of the sinuses and the long bones were normal. Urinalyses always gave normal results. The reactions to Mantoux tests with 0.1 and 1 mg. of tuberculin were negative. The cultures of material from the nose and throat revealed nonhemolytic Staphylococcus aureus and nonhemolytic streptococcus. Paul-Bunnell tests on October 1, October 17 and November 7 all gave negative results. The course in the hospital was uneventful. The highest temperature was 37.6 C. (99.7 F.).

TABLE 2.—*Hematologic Data for J. G. (Case 2)*

Age, Years	Date	Hemoglobin Content, Gm. per 100 Cc.	Red Cells, Millions per Cu. Mm.	Packed Red Cell, Volume per Cent	White Cells, per Cu. Mm.	Neutrophils				Lymphocytes		Monocytes, Percentage	Eosinophils, Percentage	Basophils, Percentage	Result of Paul-Bunnell Test
						Percentage	Number	Band	Segmented	Percentage	Number				
First Hospitalization, 12/8/38 to 1/8/39															
1½	12/ 8/38	12.0	4.20	..	16,000	61	9,760	8	53	37	5,920	2	..	..	.....
	12/29	....	....	..	20,100	67	13,467	8	59	33	6,633	..	..	..	.....
	1/ 8/39	11.5	4.00	..	18,200	58	10,556	8	50	42	7,644	..	..	..	.....
Second Hospitalization, 12/30/39 to 1/11/40															
2½	12/30/39	14.0	5.20	..	28,000	85	23,800	23	62	15	4,200	..	..	..	.....
	1/ 2/40	....	....	..	16,400	64	10,496	17	47	31	5,084	5	..	..	.....
	1/ 9	....	....	..	8,800	50	4,400	19	31	43	3,784	7	..	..	.....
Third Hospitalization,* 9/26/40 to 10/7/40															
3⅛	9/26	(82%)	4.12	..	98,000	19	18,620	0	19	82	80,360†	..	..	..	.....
	9/28	11.0	4.70	..	59,000	9	5,310	0	9	86	50,740	2	4	..	.....
	10/ 1	....	....	..	.....	..	.....	..	..	..	.....	..	..	..	Negative
	10/ 7	....	....	..	70,050	12	8,406	2	10	80	56,040	2	6	..	.....
Outpatient Studies, 10/11/40 to 11/17/40															
	10/11	11.0	4.40	..	26,000	13	3,380	0	13	83	21,580	2	2	..	.....
	10/15	13.0	4.61	36	22,250	21	4,672	3	18	72	16,020	5	2	..	.....
	10/17	....	....	..	.....	..	.....	..	..	..	.....	..	..	..	Negative
	11/ 4	11.0	4.41	..	10,000	23	2,300	0	23	71	7,100	2	3	1	.....
	11/17	....	....	..	.....	..	.....	..	..	..	.....	..	..	..	Negative
Fourth Hospitalization, 11/14/40 to 11/23/40															
	11/16	12.0	....	39	10,100	33	3,333	1	32	59	5,959	5	3	..	.....
	11/20	....	....	..	16,500	46	7,590	21	25	45	7,425	1	6	2	.....
Outpatient Studies, 12/3/40 to 3/11/41															
	12/ 3/40	14.0	5.10	40	15,000	29	4,350	2	27	60	9,000	1	9	1	.....
	12/17	13.6	5.10	40	15,400	62	9,548	9	53	30	4,620	8	..	..	.....
4⅝	1/28/41	13.5	5.80	39	14,600	30	4,200	1	29	61	8,540	3	5	1	.....
	2/25	13.0	5.80	38	18,000	30	5,400	1	29	64	11,520	4	2	..	.....
	3/11	13.5	5.20	40	17,100	24	4,104	2	22	69	11,799	2	5	..	.....

* The child was hospitalized at another institution from Sept. 26 to Oct. 7, 1940. All other admissions were to the New York Hospital, and all outpatient studies were carried out at that institution.

† These cells were not identified at this time but were subsequently classified as lymphocytes.

The results of examinations of the blood during this and the two previous hospitalizations are included in table 2. It will be noted that examination in the outpatient department revealed a moderate elevation of the white cells with lymphocytosis. The only physical signs of note were the presence of injected and hypertrophied tonsils and a postnasal drip. The child's appetite was poor; he looked pale, and he complained of vague paraumbilical pain. At the last examination, on March 11, 1941, the temperature was 38 C. (100.4 F.).

Aspiration and examination of sternal bone marrow on Nov. 16, 1940 revealed a total count of 110,000 nucleated cells and 56 megakaryocytes per cubic millimeter. The differential count showed the following distribution: neutrophilic band forms, 11 per cent; segmented forms, 20 per cent; lymphocytes, 30 per cent; eosinophils, 3 per cent; neutrophilic myelocytes, 10 per cent, and nucleated red cells, 15 per cent. Except for an increase in the number of normal-appearing lymphocytes, the total count and the differential smear were normal.

In the cases of 2 children, 3½ and 6 years of age, there was unexpected and exaggerated lymphocytosis, with maximum leukocyte counts of 98,000 and 44,300 cells per cubic millimeter, respectively. The course in each was benign, and in neither was there lymphadenopathy, enlargement of the spleen or the clinical or physical signs characteristic either of infectious mononucleosis or of leukemia. The examination of sternal marrow ruled out leukemia, and the blood picture could be readily differentiated from that of infectious mononucleosis or leukemia. In neither cases did the Paul-Bunnell test ever give positive results.

In each case there had been two earlier hospitalizations, and on these occasions there had been a moderate leukocytosis with a neutrophilic response. After subsidence of the hyperleukocytosis, each child eventually showed a moderate elevation of the white cells with an absolute increase in the lymphocytes. In both cases nasopharyngitis was associated with this blood response as well as the other complaints which characterized the second group of cases, to be described. Bacteriologic studies revealed the same types of organisms during every hospitalization, but these could not be correlated with the type of blood response.

GROUP 2: CHRONIC INFECTIOUS LYMPHOCYTOSIS

Only 1 case will be described in detail; 8 others are briefly summarized in table 3. The patients in cases 3 and 4 were observed in the hospital, and the remainder were seen either in the outpatient department or as private patients.

CASE 3.—A. van K., a 1 year old girl, was admitted to the hospital on Sept. 5, 1940 because of irregular, low grade fever, of five months' duration. In April 1940, without an antecedent history of an acute infection, it was observed that she had an elevated temperature. Subsequently, and until the time of admission, the infant's temperature fluctuated between 37.5 and 38.7 C. (99.5 and 101.7 F.), and sometimes reached 39 C. (102.2 F.). Physical examination during this time revealed that the ears, the nose and throat and the heart and lungs were normal.

TABLE 3.—*Data for Nine Cases of Chronic Infectious Lymphocytosis*

Case No., Name, Age	Date	Hemoglobin Content, Gm. per 100 Cc.	Red Cells, Millions per Cu. Mm.	Packed Red Cell Volume per Cent	White Cells, per Cu. Mm.	Neutrophils: Percentage	Neutrophils: Number	Neutrophils: Band	Neutrophils: Segmented	Lymphocytes: Percentage	Lymphocytes: Number	Monocytes, Percentage	Eosinophils, Percentage	Basophils, Percentage	Result of Paul-Bennell Test	Comment
	1940															
Case 3	4/15	10.4	4.42	..	11,400	14	1,596	0	14	77	8,778	7	1	1	.....	See text
A. van K.	9/ 5	11.5	4.00	..	11,000	33	3,630	2	31	60	6,600	3	3	1	.....	
7 mo.	9/ 9	12.0	4.50	..	8,500	14	1,190	1	13	85	7,225	..	..	..	.....	
	9/17	12.2	4.88	..	11,800	18	2,124	3	15	78	9,204	3	1	..	.....	
	9/18	....	....	..	.....	..	.....	..	..	..	.....	..	..	..	Negative	
	9/19	....	....	..	14,000	16	2,240	1	15	80	11,200	3	1	..		
	1940															
Case 4	11/ 5	13.0	4.60	..	14,800	23	3,404	18	5	66	9,768	11	..	..	.....	Admitted March 5, 1940 with fever and vomiting of 4 days' duration; highest temperature 40.8 C. (105.4 F.); enlarged injected tonsils and postnasal discharge; liver and spleen not palpable; no lymphadenopathy; cultures of material from nose and throat: Staphylococcus aureus haemolyticus, nonhemolytic streptococcus, pneumococcus. After discharge on Nov. 10, 1940 temperature did not return to normal; on March 27, 1941 it still ranged between 100 and 101 F. Sedimentation rate normal Jan. 21, 1941
E. B.	11/ 9	9.5	....	34	14,800	38	5,264	16	22	59	8,732	3	..	..	.....	
11 mo.	11/10	....	....	..	.....	..	.....	..	..	..	.....	..	..	..	Negative	
	11/19	11.6	3.776	35	9,800	16	1,568	1	15	81	7,938	3	..	..		
	12/ 1	11.2	5.168	..	13,600	16	2,176	0	16	75	10,200	7	1	1	.....	
	1941															
	1/12	12.0	5.216	..	13,800	12	1,656	2	10	85	11,730	3	..	..	.....	
	3/12	11.0	4.592	40	13,500	13	1,755	3	10	80	10,800	6	1	..	.....	
	3/27	11.0	4.12	39	12,800	23	2,944	3	20	71	9,088	4	2	..	.....	
	1938															
Case 5	12/30	10.8	3.60	..	14,000	22	3,080	6	16	71	9,940	2	3	2	.....	For 1 year after an attack of tonsillitis temperature ranged from 100 to 101 F.; tonsils markedly hypertrophied and injected; cervical nodes alone enlarged, spleen not palpable. Between Nov. 9, 1938 and March 6, 1940 5 blood counts made; highest showed 23,200 white cells per cu. mm. with 75 per cent lymphocytes; lymphocytes predominated in all except last count, in which white cells numbered 11,200 with 25 per cent lymphocytes. Sedimentation rate slightly elevated Jan. 30, 1938
R. B.																
19 mo.																
	1940															
Case 6	3/ 7	11.5	4.00	..	5,600	8	448	0	8	89	4,984	2	..	..	.....	Paraumbilical pain, anorexia and low grade fever for 2 months; tonsils moderately enlarged and injected. Postnasal discharge but no lymphadenopathy; spleen not palpable. Abdominal pain gradually subsided and appetite returned
L. G.	3/19	13.0	4.86	40	12,850	41	5,268	6	35	55	7,067	3	1	..	.....	
3 yr.	3/21	....	....	..	.....	..	.....	..	..	..	.....	..	..	..	Negative	
	5/21	14.0	5.18	..	15,900	25	3,975	2	23	72	11,448	2	1	..		
	7/ 2	15.0	5.33	40	12,500	15	1,875	1	14	83	10,375	1	1	..	Negative	
	1940															
Case 7	8/24	11.8	....	..	7,900	21	1,659	0	21	77	6,083	1	1	..	.....	Paraumbilical pain, anorexia and lassitude following acute infection of upper respiratory tract 3 weeks previously. Tonsils markedly hypertrophied and injected; few cervical nodes slightly enlarged; liver and spleen not palpable. Tonsillectomy in September 1940, with relief of symptoms until December 1940, when infection of upper respiratory tract occurred, followed by slightly elevated temperature for 1 month; pharyngeal injection and postnasal discharge present. Roentgen examination in January 1940 showed involvement of one antrum and both ethmoid sinuses. Sedimentation rate normal Aug. 24, 1940 and Jan. 30, 1941
H. F.	1941															
4 yr.	1/16	....	....	..	15,000	36	5,400	1	35	55	8,250	6	2	1	.....	
	1/30	11.8	....	..	10,900	33	3,597	0	33	64	6,976	2	1	..	.....	

	1940															
Case 8	9/11	11.8	....	..	11,600	25	2,900	1	24	73	8,468	2	..	..	.....	Severe paraumbilical pain for 3 weeks preceding acute infection of upper respiratory tract with temperature of 104 F.; subsequent persistent low grade fever; temperature ranging from 100 to 101 F. still present 6 months later (March 25, 1941). Tonsils markedly hypertrophied and injected; heavy postnasal discharge; cervical nodes slightly enlarged; liver and spleen not palpable. Abdominal pain less severe but has not subsided entirely. Sedimentation rate normal Feb. 5, 1941
J. G.	9/19	11.2	....	..	14,600	35	5,110	1	34	59	8,614	4	1	1	.....	
4 yr.	1941															
	2/ 5	12.6	5.008	40	13,600	27	3,672	2	25	72	9,792	1	..	..	.....	
	2/ 8	12.6	....	..	14,300	46	6,578	4	42	51	7,293	2	1	..	.....	
	3/24	12.4	4.80	..	9,100	21	1,911	3	18	75	6,825	2	1	1	.....	
	3/25	....	....	..	.....	..	.....	..	..	..	.....	..	..	..	Negative	
	1940															
Case 9	5/18	....	....	..	.....	..	.....	..	..	..	.....	..	..	..	Negative	Over a 4 year period temperature has ranged between 99 and 101 F.; with acute colds rises to 103 F. Tonsils removed at 3 years of age. Postnasal discharge noted in several examinations; no lymphadenopathy; spleen not palpable. Results of urinalyses, Mantoux tests with up to 1.0 mg. of tuberculin and bacilli agglutination tests for Brucella and typhoid all negative. Roentgen examination Dec. 2, 1940 showed involvement of right ethmoid and both maxillary sinuses. Temperature gradually declined to normal. Sedimentation rate normal May 8, 1940
S. B.	5/25	14.0	....	42	6,500	24	1,560	1	23	71	4,615	4	1	..		
7½ yr.	11/23	14.0	....	40	6,100	40	2,440	2	38	52	3,172	5	3	..	.....	
	12/ 7	13.0	....	43	8,400	35	2,940	3	32	53	4,452	7	3	2	.....	
	1939															
Case 10	11/29	11.0	4.41	..	9,000	22	1,980	0	22	78	7,020	..	..	..	.....	Failure to gain weight, lassitude, headache, occasional joint pains over 2 year period. Temperature recorded for 1 week trial period in December 1939 ranged from 99 to 101 F. Tonsils large and injected; heart and lungs normal; lymph nodes small and palpable in cervical, axillary and inguinal regions; spleen palpable only once. Roentgenogram of chest normal. Four determinations of sedimentation rate between Nov. 22 and Dec. 29, 1939 normal; reaction to repeated Mantoux tests negative; electrocardiogram normal. Gradual subsidence of symptoms during period of observation
J. M.	12/15	11.8	4.562	36	8,000	37	2,960	0	37	60	4,800	2	1	..	.....	
9 yr.	1940															
	1/ 2	12.0	4.02	36	8,800	46	4,048	13	33	43	3,784	5	6	..	.....	
	1/ 4	....	....	..	.....	..	.....	..	..	..	.....	..	..	..	Negative	
	4/16	12.5	4.61	..	8,600	61	5,246	0	61	37	3,182	1	1	..		
	1940															
Case 11	4/19	13.5	....	..	5,600	33	1,848	5	28	48	2,888	13	6	..	Negative	Acute infection of upper respiratory tract 11 weeks before first examination; since then temperature elevated up to 101 F.; fever especially noticeable after activity; headache and abdominal pain occasionally noted. Tonsillectomy in 1933. Mass of hypertrophied follicles in posterior pharyngeal wall; no adenopathy and spleen not palpable; normal roentgenograms of sinuses; results of tuberculin tests and agglutination tests for typhoid, paratyphoid, brucella and typhus organisms negative; sedimentation rate always normal; electrocardiogram normal March 23 and Aug. 21, 1940
E. S.	6/10	13.0	....	..	7,750	37	2,868	0	37	55	4,263	0	4	..		
11 yr.	6/15	....	....	..	.....	..	.....	..	..	..	.....	..	..	..	Negative	
	6/21	14.0	4.34	..	8,200	45	3,690	0	45	37	3,034	0	13	..		
	10/ 2	13.0	4.60	..	12,200	41	5,002	0	41	56	6,832	0	3	..	.....	
	12/17	12.0	....	..	9,550	32	3,056	0	32	64	6,112	..	..	..	.....	

Small lymph nodes were palpable in the neck and in the submental and the inguinal regions. The liver and the spleen were also felt. Only during a short period of treatment with sulfapyridine (2-[paraaminobenzenesulfonamido] pyridine) did the temperature become normal, and it rose again when administration of the drug was stopped. A large number of tests were performed in an endeavor to discover the source of infection. The Wassermann and Kline reactions of the mother and the child were negative. Urinalyses, tuberculin tests, roentgen examination of the chest, blood cultures, examination of the gastric contents for tubercle bacilli and tests for typhoid, paratyphoid A and B and brucella organisms all gave negative results. The only observations of note were mild anemia and a preponderance of lymphocytes in the blood smear.

On admission to the hospital the infant did not appear acutely ill, and physical examination revealed no outstanding abnormalities. Small, shotty glands were felt in the left anterior cervical, submental and right ingunial regions. The tonsils were not enlarged, but the anterior pillars were injected. The heart and the lungs were normal. The edge of the liver was 1 fingerbreadth below the costal margin, and the spleen and the kidneys could not be palpated. On September 18 it was noted that the tonsils were deeply injected.

During the stay in the hospital repeated urinalyses always gave normal results and excretory urograms revealed no obstruction in the upper part of the urinary tract. The roentgenogram of the chest was normal. Cultures of material from the nose and throat showed hemolytic Staph. aureus, Pneumococcus, nonhemolytic streptococcus and diphtheroid bacilli. The Paul-Bunnell test on September 8 was negative. The course in the hospital was uneventful, and during the sixteen days of observation the temperature rose slightly on one day to 37.6 C. (99.7 F.) and was normal on all other days. Examination of bone marrow obtained by sternal aspiration on September 19 showed 92,500 nucleated cells and 100 megakaryocytes per cubic millimeter. The differential count was as follows: neutrophilic band forms, 8 per cent; segmented forms, 8 per cent; lymphocytes, 50 per cent; eosinophils, 2 per cent; myeloblasts, 1 per cent; neutrophilic myelocytes, 11 per cent; eosinophilic myelocytes, 1 per cent; metamyelocytes, 4 per cent, and nucleated red cells, 15 per cent. Except for the increase in lymphocytes the differential count was normal. The results of blood studies are noted in table 3. A record from the referring physician showed that on May 31 the white count was 7,700 per cubic millimeter, with 81 per cent lymphocytes.

Summary of Cases in Group 2.—The cases presented were chosen from a much larger number to illustrate typical clinical features and blood reactions. The common complaint was persistent low grade fever dating back to a well defined acute infection of the upper respiratory tract. The symptoms were more conspicuous in the children under 6 years of age (cases 3 to 8) than in the older ones (cases 9 to 11). In the former cases there was an absolute increase in the lymphocytes, as compared with a relative increase in the latter. In case 9, however, that of an older child, the febrile reaction had persisted for four years, and the child had undergone numerous examinations by many physicians in an attempt to determine the source of the infection. In several cases the presence of a preponderance of lymphocytes, which sometimes stained abnormally instead of giving an expected neutrophilic response, led the

attending physicians to suspect the existence of a blood dyscrasia. In the cases in group 2, as in the cases of the acute form of the disease in the first group, the outlook was always favorable and the condition could be differentiated from infectious mononucleosis and leukemia.

ANALYSIS OF THE CASES

CLINICAL FEATURES

The cases in group 1 can be differentiated from those in group 2 in that they were characterized by a more striking leukocytosis of shorter duration and a greater lymphocytic preponderance. The sharp rise in lymphocytes was unexpected and did not conform to the characteristics of any well defined disease. In neither case were there any complaints or abnormal physical signs, such as enlargement of the lymph nodes or the spleen, hemorrhagic manifestations or a febrile reaction.

The complaints in the cases of the second group are readily recognized as those commonly encountered in pediatric practice. The most prominent of these was the persistence of a slight elevation of temperature, up to 101 F., after an acute infection of the upper respiratory tract or the throat. Associated with the febrile disturbance were anorexia, pallor, loss of energy, irritability, fatigability, abdominal pain, which was localized to the region of the umbilicus, and, rarely, vague pains in the joints. Nausea and vomiting of mucus were common, occurred usually in the morning on rising and often followed a period of coughing, in which the attempt was made to clear the nose and throat. It was significant that the vomiting was not associated with the abdominal pain, for while the former occurred usually in the morning the latter was noted intermittently during other periods of the day.

Physical examination usually revealed a pale, listless child, who often had the appearance of being chronically ill. The fauces were injected, the tonsils when present were usually greatly hypertrophied, postnasal discharge was frequent and a foul odor could often be detected from the nose. Infrequently, the superficial lymph nodes, especially in the cervical region, were slightly enlarged. The abdomen in all cases was soft, flaccid and not tender, and rectal examination revealed no abnormalities. In infants the edge of the spleen was occasionally palpable, but this sign was inconstant. In case 10, that of an older child who had a history of symptoms of two years' duration, the edge of the spleen was palpated only once, and this toward the termination of her illness. In no case was the heart ever enlarged, the sounds were always normal, and the electrocardiographic tracings, when obtained, were always normal. In only 1 instance (case 6) was a soft systolic murmur heard; this was observed at the first examination, and it disappeared subsequently and did not return. In no case was there anything in the history or the results of

the physical examination and the tests to suggest tuberculosis. The results of urinalyses were always normal, and the sedimentation rate also was usually within the range of normal. The outlook was always favorable, and in every instance there was eventually a gradual subsidence of the symptoms, some of which appeared to be influenced by appropriate therapy. Treatment was symptomatic and was also directed toward the relief of infection in the upper respiratory tract.

Abdominal pain was such a disconcerting complaint in the younger patients with the chronic form of the disorder that its relation to the syndrome may be discussed more fully at this point. Abdominal pain in childhood results from various causes, but its dependence on mesenteric and retroperitoneal lymphadenitis associated with infections of the throat has frequently been emphasized.[6]

In one group of cases recently reported as instances of nonspecific mesenteric lymphadenitis,[7] the blood counts showed moderate leukocytosis with an increase in polymorphonuclear neutrophils. In the majority of these cases definite abdominal tenderness was noted, and in some spasm and rigidity were observed in the right iliac region. At operation the outstanding observation was acutely inflamed and swollen mesenteric nodes.

In the group of cases under discussion here the pain was of varying severity—intermittent, colicky or mild—and was referred to the region of the umbilicus. The abdomen was always soft, and no tenderness was elicited. The blood count showed a lymphocytic reaction, in contradistinction to the neutrophilic response in the group of cases of nonspecific mesenteric lymphadenitis. It is conceivable that in some cases the mesenteric lymph nodes may become hyperplastic and that such hyperplasia may be associated with a lymphocytic blood reaction comparable to that accompanying similar involvement of lymph nodes elsewhere. This seems the more likely since infections of the respiratory tract in the earlier period of life appear to involve the lymphatic system more regularly than do similar infections in older persons. It is possible that the blood smear may serve as a diagnostic criterion for the separation of suppurative and nonsuppurative infection of the mesenteric lymph nodes.

That other factors may be involved in the causation of abdominal pain is suggested by those instances in which a profuse postnasal discharge occurred. In the chronic group of cases it was noted that treatment of the nasopharynx appeared to relieve vomiting which occasionally occurred, and often relieved the abdominal pain. It does not appear

6. Brennemann, J.: Abdominal Pain of Throat Infections, Am. J. Dis. Child. **22**:493 (Nov.) 1921.

7. Sobel, I. P., and Stetten, DeW.: Nonspecific Mesenteric Lymphadenitis: Report of Fifty-Eight Cases, J. Pediat. **17**:305 (Sept.) 1940.

likely that swelling of the mesenteric nodes would subside so rapidly, and this observation points rather to the possibility that in some instances, at least, the constant ingestion of mucus leads to discomfort in the gastrointestinal tract.

THE BLOOD PICTURE AND APPEARANCE OF THE BONE MARROW

Red Blood Cells and Hemoglobin Content.—In the cases of group 1, no anemia was noted during the period of marked leukocytosis. In the second group, while the red cell and hematocrit values were normal, a lowered hemoglobin content was noted in cases in which the symptoms had persisted for a long time, especially when the patient was an infant or a younger child. The values for hemoglobin approximated the lower limit of normal but did not fall within the distinctly abnormal range. At the height of the severe infection, however, as was observed in case 4, the hemoglobin content and the red cell count were considerably reduced. The platelets always appeared in normal numbers, and no change in the bleeding or the clotting time was observed.

White Blood Cells.—Striking abnormalities in the total white cell count and in the differential percentages characterized the blood picture of the cases in group 1. White cell counts of 39,000 to 44,300 in case 1, with 60 to 79 per cent lymphocytes, and of 59,000 to 98,000 in case 2, with over 80 per cent lymphocytes, constitute examples of hyperleukocytosis with exaggerated lymphocytosis. Numerical deviations from the normal were not so conspicuous in the cases of group 2. In the 9 cases illustrative of this group, in which the clinical course was prolonged, the degree of abnormality of the blood reaction could only be gaged by comparing the total white cell count and the differential percentages with the maximal normal values cited earlier.

Since the shift from lymphocytic to granulocytic predominance occurs normally at from 3 to 5 years of age, the cases of the second group may be subdivided further by considering cases 3 to 8, inclusive, in which the patient was below 5 years of age, separately from the last 3 cases, in which the patient's age ranged from 7½ to 11 years. The total white cell counts for the younger group of patients ranged from 5,600 to 15,900 per cubic millimeter, and in 20 of 25 determinations the leukocyte count exceeded 10,000 per cubic millimeter. In 23 of 25 blood smears of the younger children, the absolute number of lymphocytes exceeded the maximal normal values of 7,000 per cubic millimeter for subjects 1 to 2 years of age and of 6,000 for those 3 to 4 years of age. For the 3 children ranging from 7½ to 11 years of age, the white cell counts ranged from 5,600 to 12,200 per cubic millimeter, but in 11 of 12 counts the totals fell within the range of normal. In only 3 counts did the absolute values for lymphocytes exceed the level of 6,000 per cubic millimeter. In 8 of 12

instances, however, the relative proportion of lymphocytes was increased to above 50 per cent of the total. Two of the 4 counts in which the proportion of lymphocytes was below 50 per cent were made in case 10 and were obtained in the latter part of the illness, when recovery was in progress. The absolute number of neutrophils was decreased below 3,000 per cubic millimeter in 21 of 37 examinations of the blood made in the cases of group 2. Except in 2 counts made during a severe febrile reaction in case 4, band forms were not increased, and normal segmented neutrophils characterized the blood smears.

The possibility of an underlying pathologic condition affecting hematopoiesis was suggested at some time in all of the cases. In the cases of the acute form of the disease this would be expected because of the

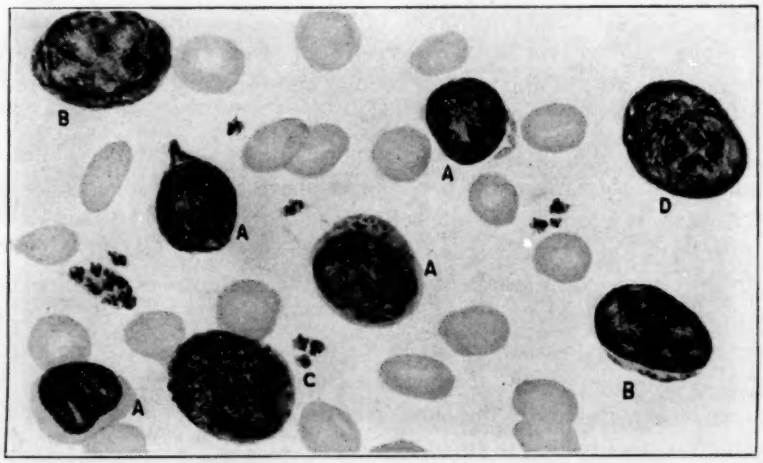

Fig. 1.—Drawings of cells commonly found in cases of infectious lymphocytosis. The majority of the cells are normal lymphocytes, represented by *A* and *B*. *B*, *C* and *D* are larger cells, but *C* and *D* typify the small percentage of cells in the smear which show morphologic changes. The nucleus of *C* stains less intensely than that of the other cells. The cytoplasm of *D* stains deeply, and its nucleus is eccentric. A characteristic feature of most of the lymphocytes, large and small alike, is the increased basophilia of the cytoplasm.

hyperleukocytosis. In the cases of the chronic form of the disorder the persistence of the symptoms, the absence of the expected neutrophilic response, the absolute or the relative increase in lymphocytes and the presence of morphologic changes in certain of the cells usually led to a consideration of the diagnosis of infectious mononucleosis and, less often, to that of leukemia.

The Blood Smear.—The cytologic changes which are of diagnostic value apply only to the lymphocytes and are illustrated in figure 1.

The lymphocytes were mainly of the small and intermediate varieties and were characteristically of uniform size and normal structure (fig. 1 *A* and *B*). The nucleus possessed the coarse, chromatin masses of the normal mature lymphocyte, and the cytoplasm was usually scant but moderately to deeply basophilic. The deeper stain of the cytoplasm constitutes the most important diagnostic feature of the lymphocytes in this group of cases. In addition, a few cells of the larger variety (fig. 1 *D*) were frequently encountered; they were of normal shape and had a cytoplasm possessed of deep basophilia and a nucleus which was often eccentric and stained more intensely than that of the normal lymphocyte. Another type of lymphocyte (fig. 1 *C*), which was about one and a half times the size of a red cell, possessed a narrow margin of deeply basophilic cytoplasm but a nucleus which was round, oval or slightly indented and stained less intensely than that of the normal cell. The larger cells usually did not exceed 5 per cent of the total except in the cases of infants with the chronic form of the disorder, in which they were more numerous. In the latter cases, also, the zone of cytoplasm of the cells was often wider and the basophilia deeper than in the corresponding cells of older children. Such larger cells (fig. 1 *C* and *D*) cannot be regarded as specific, because they may occasionally be found in the blood of normal infants and also appear in increased numbers in the blood of infants and young children during the course of a large variety of infections, both in the active stages and during convalescence. The lymphocytes in the blood in the series of cases under discussion did not possess the irregularity of shape and the abundant, frequently vacuolated and foamy cytoplasm (fig. 2 *G*) which are distinctive features of certain of the cells in infectious mononucleosis.

The Bone Marrow.—Bone marrow was aspirated in 3 cases. The myeloid elements and the nucleated red cells were normal in number, but the lymphocytes were increased above normal. In cases 1 and 2, in which hyperleukocytosis was present in the peripheral blood, the lymphocytes numbered 36 and 30 per cent, respectively. In these 2 cases the bone marrow was aspirated during the period when the leukocyte count in the peripheral blood was falling. In case 3, of the chronic group, the lymphocytes represented 50 per cent of the cells. In all 3 cases, therefore, the lymphocytes were increased, and except for an occasional cell with increased basophilia they were of the normal small variety.

DIFFERENTIAL DIAGNOSIS

The two groups of cases described in this paper have been considered together because of several features which they possessed in common. In both a conspicuous feature of the blood picture consisted of a preponderance of lymphocytes. In the first 2 cases an unexpected and sudden hyperleukocytosis occurred, but the patients were afebrile and there was

no enlargement of the spleen or the lymph nodes. The blood counts eventually dropped to more normal levels, but later studies again revealed leukocytosis with a lymphocytic preponderance corresponding numerically and qualitatively to that of the cases of group 2, in which the disease was chronic. When this occurred moderate pharyngitis was noted, as well as some of the other symptoms observed in the cases of the chronic group. It is noteworthy that each of the patients had had two previous hospital admissions and in each instance the blood showed leukocytosis with a neutrophilic response.

In the cases of the second group there was an acute infection of the upper respiratory tract at the onset, which was followed by a period of chronic illness during which there were varied complaints, consisting principally of low grade fever, anorexia and abdominal pain. In all cases inflammation of the pharynx and postnasal drip were the most common signs, and in them, too, there was no conspicuous lymphadenopathy and usually no enlargement of the spleen. The characteristic feature of the blood response in this group was a moderate leukocytosis with an increase in lymphocytes. Whether the factor responsible for the blood reaction is associated with pharyngitis awaits further study. Such a relation seems plausible for the chronic group and uncertain for the acute group, in which physical signs were lacking.

Since in all of the cases at some time or other infectious mononucleosis and leukemia were considered in the diagnosis, these two conditions will be given primary consideration.

Infectious Mononucleosis.—Infectious mononucleosis in children, as in adults, is an acute infectious disease which occurs epidemically or sporadically and is characterized by a prodromal period of malaise, anorexia and listlessness followed by fever, pain in the back of the neck, enlargement and tenderness of the lymph nodes, sore throat, enlargement of the spleen and characteristic blood changes which chiefly affect the lymphocytes. The febrile phase usually lasts one to three weeks and then subsides, although enlargement of the glands and the spleen may persist. In chronic infectious lymphocytosis, on the other hand, the acute symptoms are usually milder and of shorter duration and in contrast to infectious mononucleosis, they persist, accompanied by low grade fever, for months.

The discovery by Paul and Bunnell [8] that the blood serum of patients with infectious mononucleosis is able to clump sheep red cells in dilutions considerably above the normal titer introduced an important diagnostic measure. Numerous studies have confirmed the specificity of the heterophile antibody test, and by means of appropriate absorption tests

8. Paul, J. R., and Bunnell, W. W.: The Presence of Heterophile Antibodies in Infectious Mononucleosis, Am. J. M. Sc. **183**:90 (Jan.) 1932.

it is possible to exclude the elevated titers sometimes encountered in normal persons and in those with serum sickness. Titers of 1 : 56 to 1 : 112 have been regarded as indicating a borderline result [9] and those of 1:160 or more as indicating a significantly positive reaction.[10] The incidence of positive reactions in cases of infectious mononucleosis has varied, however, in different clinics, and by some it has been claimed that positive results from the test are obtained in less than 50 per cent of cases.[11]

The Paul-Bunnell test was performed in all cases in this series except 5 and 7, in which the clinical picture and the course conformed unmistakably to those characteristic of a persistent infection of the upper respiratory tract. In the 7 remaining cases of the chronic group and in cases 1 and 2 of the acute group, the heterophile antibody reaction was uniformly negative.

In those cases of infectious mononucleosis in which the clinical picture is equivocal the morphologic character of the mononuclear cells serves as a more important differentiating factor. The classification of the cells is attended with difficulty but supravital studies have established their identity as lymphocytes, although the monocytes may also be increased. The characteristic mononuclear cells are atypical and possess morphologic features which distinguish them from the cells found in the cases described in this paper. They are larger than normal, their cellular edges are often ragged and irregular (fig. 2 *F*) and the cytoplasm is usually abundant and stains darker blue with the Wright stain than do normal large lymphocytes. The shade varies from slate color to the deep blue of a plasma cell; there may be a perinuclear zone which stains more lightly than the margin of the cell (fig. 2 *K*), and in some instances the stain is concentrated at the periphery of the cell (fig. 2 *F*). The cytoplasm contains fine or coarse azure granules, and one of the most striking features is vacuolation. The vacuoles are of two types. They may be large and scattered in a cell with abundant cytoplasm (fig. 2 *E*), or they may be smaller and more numerous (fig. 2 *G*). The combination of fine vacuolation and basophilia gives the cytoplasm a foamy appearance (fig. 2 *G*), which is a striking and distinctive feature of the cell in infectious mononucleosis. Such cells correspond to those which were observed by Gall and Stout [12] in the lymph nodes in cases of infectious mononucleosis

9. Davidsohn, I.: Serologic Diagnosis of Infectious Mononucleosis, J. A. M. A. **108**:289 (Jan. 23) 1937.

10. Bernstein, A.: Infectious Mononucleosis, Medicine **19**:85 (Feb.) 1940.

11. Vogel, P., and Bassen, F. A.: Sternal Marrow of Children in Normal and in Pathologic States, Am. J. Dis. Child. **57**:245 (Feb.) 1939.

12. Gall, E. A., and Stout, H. A.: The Histological Lesion in Lymph Nodes in Infectious Mononucleosis, Am. J. Path. **16**:433 (July) 1940.

and which they regarded as the feature most nearly pathognomonic of this disease. In the other cells the cytoplasm is a uniform deep blue (fig. 2 *H*), the most distinctive shades with Wright's stain being sky blue or cobalt blue.

The nucleus may be round, oval or kidney shaped; occasionally it is divided and it is often eccentrically placed. The chromatin may consist of deeply stained, clumped masses, as in the normal lymphocyte. In some the nuclear pattern is coarser than normal, and in others it is more immature in that the chromatin consists of finer strands, which are demarcated from the parachromatin and stain more lightly. Rarely, an immature lymphocytic cell (fig. 2 *K*) is encountered, with a lightly staining nucleus

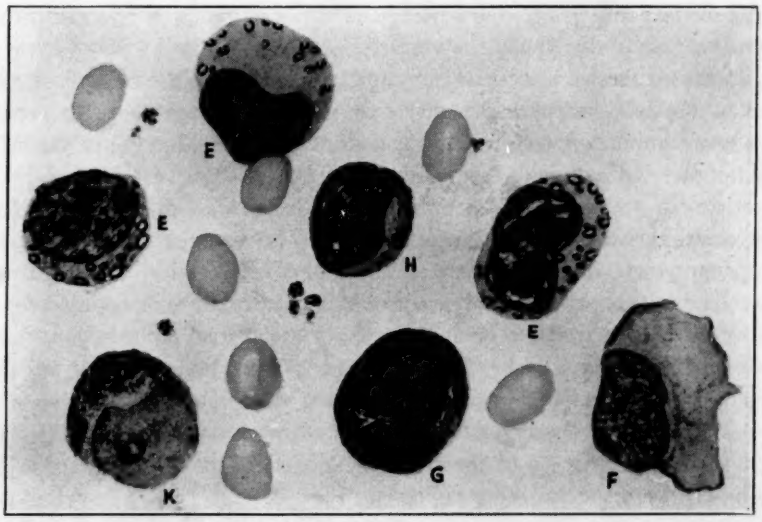

Fig. 2.—Drawings of representative cells found in cases of infectious mononucleosis occurring in childhood. Although a number of different types usually appear in the blood smear at one time, especially at the height of the disease, all of these cells did not occur together in any single case. *F* shows a cell with irregular edges, eccentric nucleus, abundant cytoplasm and concentration of basophilia in the periphery. A lightly staining perinuclear zone is observed in *K*. Deep basophilia of the cytoplasm is noticeable in *G*, *H* and *K*. Vacuolation of the cytoplasm is present in *E* and *G*. The finer vacuoles and deep basophilia in *G* give the cytoplasm a foamy appearance, which is an important diagnostic feature. Cells of type *K* occurred most infrequently. The nucleus of *K* stains lightly and approaches in immaturity the nucleus of the lymphoblasts (*L*) in figure 3.

the chromatin of which is finely divided and which possesses one or more nucleoli. The nucleus of such a cell, however, is usually not as leptochromatic and not as finely stippled as that of the lymphoblast of leukemia, and the cytoplasm is more abundant (fig. 3 *L*). The fenestration, or

holes, in the nuclei of the lymphocytes which were described by Osgood [13] as peculiar to infectious mononucleosis have only occasionally been observed in my cases. In the acute stages of infectious mononucleosis the diagnosis is made not by the presence of a single type of cell suggestive of the disease but by the assortment of unusual cells in the entire blood smear. The diverse shapes and sizes of the mononuclear elements, the varied shades of blue in the cytoplasm and the difficulties often encountered in differentiating between lymphocytes and monocytes in the fixed smear, all serve to separate the blood picture of infectious mononucleosis from the lymphocytic blood pictures described in this paper.

In cases 1 and 2 the lymphocytes were of the small variety and no abnormal mononunclear elements suggestive of infectious mononucleosis were present in the peripheral blood. None of the symptoms or physical signs corresponded to those of either infectious mononucleosis or leukemia. In addition, the white cell count of 98,000 per cubic millimeter in case 2 exceeds the highest number ever reported in a case of infectious mononucleosis.

The differentiation of cases of chronic infectious lymphocytosis from infectious mononucleosis may be attended with difficulty, particularly the terminal stages of the latter disease. Infectious lymphocytosis can, however, be related to a specific onset with an infection of the upper respiratory tract, and cervical adenopathy, if present, is minimal or is not more marked than occurs in most children with recurrent pharyngitis. Palpable lymph nodes anterior and posterior to the sternocleidomastoid muscle will be noted in many healthy children who have previously had attacks of nasopharyngeal infection. In the period of recovery from infectious mononucleosis careful search of the blood smear will reveal the atypical cells characteristic of this disease. Moreover, in cases of chronic infectious lymphocytosis the clinical manifestations of the disease are actively in evidence throughout the period of recovery, whereas in the comparable period of recovery from infectious mononucleosis the patient appears clinically well. In case 4, it was possible to observe the blood picture during the time of the acute infection, during convalescence and two months later. Lymphocytosis was noted when the temperature was over 104 F. as well as during the subsequent course of low grade fever.

The blood pictures in the two conditions overlap to the extent that in both small and intermediate lymphocytes with dark blue cytoplasm are present. While large basophilic cells may appear in small numbers in infectious lymphocytosis, they can readily be differentiated as lympho-

13. Osgood, E. E.: Fenestration of Nuclei of Lymphocytes: A New Diagnostic Sign in Infectious Mononucleosis, Proc. Soc. Exper. Biol. & Med. **33**:218 (Nov.) 1935.

cytes. Many of the mononuclear elements in infectious mononucleosis, however, may be so abnormal with regard to staining, structure and size that classification is difficult. The variability of the pathologic lymphocytes in the latter disease stands in marked contrast to the more uniform blood smear in infectious lymphocytosis.

The cytoplasmic basophilia of the lymphocyte in both hematologic conditions may be regarded as evidence of immaturity, although there is evidence that it may result from functional alteration.[14] In effect, the entire appearance of the lymphocytes in infectious lymphocytosis represents a shift to the left comparable to that of the polymorphonuclear cells during infection.

There is no uniformity of opinion as to the extent of infiltration of the bone marrow by the cells of infectious mononucleosis. Some observers have found no increase in lymphocytes, while others have observed large numbers of the atypical cells. As already stated, in the 3 cases of lymphocytosis described in this paper in which the bone marrow was aspirated, increased numbers of normal small lymphocytes were noted.

A group of cases in which the disease has recently been reported [15] simulated diphtheria but hematologic and serologic observations confirmed the diagnosis of infectious mononucleosis. In such cases the disease apparently belongs to the anginose type,[16] which is also known as monocytic angina. In none of the cases described in this paper, however, did pharyngitis occur in association with a membranous exudate.

Leukemia.—Leukemia in childhood may for a considerable part of its course be unassociated with enlargement of the spleen or the lymph nodes or with leukocytosis, so that the true nature of the disease is unsuspected. Both chronic infectious lymphocytosis and the initial phases of leukemia may be characterized by prolonged low grade fever, listlessness, fatigability, anorexia, abdominal pain, palpable cervical nodes and a blood smear showing a predominance of lymphocytes. While leukocytosis usually characterizes leukemia in childhood, this disease may be associated with leukopenia for a considerable part, or all, of its course.

In leukemia, however, with symptoms of the same duration as those in the cases of chronic infectious lymphocytosis of this study, the blood would have shown marked anemia, a decrease in platelets and, probably, hemorrhagic manifestations. While the hemoglobin content may be reduced in the chronic type of infectious lymphocytosis, such a reduction

14. Agress, H., and Downey, H.: The Blood Picture of Human New-Borns, with Special Reference to Lymphocytes, Folia haemat. **55**:207, 1936.

15. Werlin, S. J.; Dolgopol, V. B., and Stern, M. E.: Infectious Mononucleosis—A Diagnostic Problem, Am. J. M. Sc. **201**:474 (April) 1941.

16. Tidy, H. L.: Glandular Fever and Infectious Mononucleosis, Lancet **2**: 180 (July 28); 236 (Aug. 4) 1934.

is never as marked as in leukemia and the platelets are not decreased. Of prime importance in early diagnosis is close scrutiny of the morphologic features of the lymphocyte. Careful search of the blood smear in cases of leukemia will reveal that even with a normal white cell count occasional abnormal lymphocytes appear which possess the cytologic features of a lymphoblast. The size of this type of cell varies from that of a small lyphocyte to that of a cell at least twice as large (fig. 3 *L*). Such abnormal cells are lymphoblasts and possess certain fundamental diagnostic features. They are usually round, large and uniform in size; the narrow zone of the cytoplasm is basophilic, and when vacuoles are present

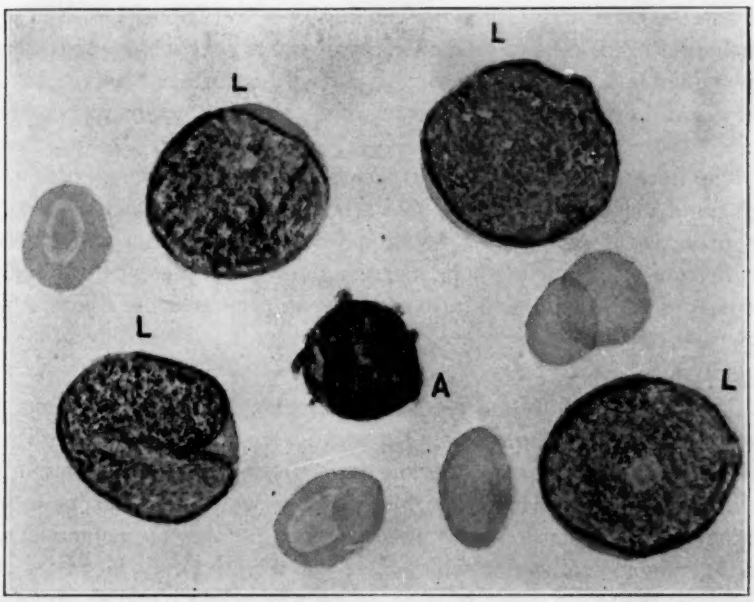

Fig. 3.—Drawings of representative cells found in the blood in the case of a 7 year old child with acute lymphatic leukemia. The large *L* cells are lymphoblasts, with scanty basophilic cytoplasm and distinctive nucleus. The nucleus in these cells stains lightly and possesses a characteristic finely granular, stippled or sievelike pattern. *A* is a normal small lymphocyte included for comparison. The *L* cells have been enlarged to bring out the finer nuclear morphologic structure.

they are two to three times the size of those in infectious mononucleosis and there are fewer of them. More important, however is the nuclear pattern. Instead of masses of dense basichromatin, such as are found in the normal lymphocyte (fig. 3 *A*), the chromatin stains lightly, is finely granular and stippled or sievelike and shows the presence of nucleoli. There is no difficulty in differentiating the average lymphocyte in infectious lymphocytosis from the lymphoblast in leukemia. The clumped

chromatin of the nucleus of the large cells of infectious lymphocytosis may be readily differentiated from the leptochromatic nucleus of leukemia.

While it is true that examination of the bone marrow would have at once eliminated leukemia as a diagnosis in the case of chronic infectious lymphocytosis this procedure could not be carried out because the patients were ambulatory and the illness did not seem of sufficient acuteness to justify hospitalization. In case 3, however, the clinical and hematologic symptoms had persisted so long that the child was admitted for observation and aspiration was performed. In the cases of hyperleukocytosis the bone marrow was examined of necessity. The lymphocytes in the marrow smear, however, in no way resembled lymphoblasts. Furthermore, the cells of the bone marrow were not completely replaced by lymphoblasts and lymphocytes, which occurs in leukemia, and the myeloid and erythroblastic elements were present in normal proportions in all cases.

The hyperleukocytosis in the first 2 cases cannot be regarded as a leukemoid reaction of the lymphoid type, for such a designation implies the presence of the specific immature cells which occur in leukemia. Neither the blood nor the bone marrow showed the presence of lymphoblasts. Since the childhood form of leukemia runs an acute course, these abnormal cells would have been present in any blood response of such a magnitude.

Miscellaneous Infections.—A large number of specific infections are associated with lymphocytosis. Typhoid fever, brucellosis and tuberculosis were excluded by appropriate tests. Lymphocytosis occurs infrequently in children with other infections in which polymorphonuclear leukocytosis is the customary type of response. Cases of pneumonia and appendicitis in childhood in which there was a lymphocytic blood reaction have been described,[17] but in spite of the misleading blood response the clinical manifestations and the physical signs in these conditions leave no doubt as to the diagnosis. A lymphocytic blood reaction with the presence of abnormal cell types resembling those in infectious mononucleosis has been described [18] at the end of the acute stage and during convalescence in cases of influenza. Postinfectious lymphocytosis persisting for a variable period has been noted not only in influenza but in a large variety of infections.

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17. Abt, A. F.: The Diagnosis of Leukemia in Childhood, M. Clin. North America **21**:89 (Jan.) 1937.

18. Joseph, S. H.: The Blood Pictures of the Infectious Diseases Occurring Primarily in Childhood, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 4, p. 2678.

In the cases with hyperleukocytosis there were no clinical manifestations of any specific infectious disease to account for the blood response. In the cases of the chronic type the disease usually began with a mild infection of the upper respiratory tract, and in case 4, in which the course was followed from the start, the outstanding feature was nasopharyngitis. The children with prolonged symptoms gave the clinical impression not of convalescence or of a postinfectious state but rather of the active continuance of a low grade infection involving the nose and throat.

Bacteriologic studies were made in a few cases and showed staphylococci, streptococci, pneumococci and diphtheroid organisms. In cases 1 and 2 cultures done in two previous hospitalizations showed approximately the same flora as was demonstrated during the third hospitalization, and yet in the first two stays in the hospital the blood showed a neutrophilic response, while in the third hospitalization of each child lymphocytosis occurred. In addition, in one of the earlier hospitalizations in case 2, in which a neutrophilic response occurred, an influenzal organism was also identified.

COMMENT

From the many different types of disorders with lymphocytic blood pictures occurring in infancy and childhood two have been segregated. In these two disorders the lymphocytes have a similar morphologic appearance, and they have been designated as acute or chronic, according to the duration and the degree of cellular response, infectious lymphocytosis. They have been differentiated clinically and hematologically from infectious mononucleosis, leukemia and specific infections with associated lymphocytosis. The acute form of infectious lymphocytosis occurs infrequently and is characterized by a remarkable outpouring of lymphocytes for a short period, whereas the chronic form is common and the cellular reaction is moderate and extends over a prolonged period.

In the 2 cases of the acute form there was transitory hyperleukocytosis with exaggerated lymphocytosis and the total white cell counts were 44,300 and 98,000 per cubic millimeter, respectively. In both instances the patients were afebrile from the start and the clinical picture did not correspond to that of either infectious mononucleosis or leukemia. In the second case, in which the more marked leukocytosis was present, the patient spent the first eleven days of his illness at another hospital, and, in the absence of sternal aspiration, he was discharged with a diagnosis of chronic lymphatic leukemia. When he was observed subsequent to discharge, the white cell count was 26,000 per cubic millimeter, with 83 per cent lymphocytes, and these cells revealed no structural evidences

of leukemia or of infectious mononucleosis. The lymphocytes were practically normal cytologically but had certain staining features which characterize the cells of infectious lymphocytosis. The physical examination also revealed no evidences either of leukemia or of infectious mononucleosis.

The lymphocytes in the cases of the chronic type were structurally similar to those in the cases of the acute type and resembled those occurring in infants and children in a variety of postinfectious states. The blood picture is nonspecific in this sense; yet in combination with the clinical picture manifested in the cases of the chronic form it constitutes a symptom complex frequently encountered in pediatric practice. This group includes the cases in which after an infection of the upper respiratory tract the patient continued to exhibit low grade fever over a prolonged period, during which anorexia, pallor, fatigability and paraumbilical pain were noteworthy accompaniments. The infants and children in this group of cases were chronically ill and were not merely recovering from an acute illness. Both the acute and the chronic form of infectious lymphocytosis offer a favorable prognosis.

It should be emphasized that a lymphocytic blood picture and the presence of basophilic lymphocytes in a child with nasopharyngitis who has a small number of palpable cervical nodes do not justify a diagnosis of infectious mononucleosis. Examination of large numbers of normal children with no sign of existing acute infection will often reveal small or moderate numbers of enlarged cervical nodes, especially the presence of a chain of small, shotty, posterior cervical nodes. Undoubtedly, such children have suffered previous repeated attacks of nasopharyngitis, and the nodes have remained somewhat enlarged. When an infection of the throat subsequently develops in such children, with or without an increase in the size of such nodes and with a lymphocytic reaction, the condition is often regarded as infectious mononucleosis, usually because of the lack of a more satisfactory classification. It is therefore pertinent to review the sequence of events leading to the present tendency to regard a wide variety of lymphocytic blood pictures in infants and in children as indicative of infectious mononucleosis and to justify a designation of another group of disorders as infectious lymphocytosis.

In the period between the description of "glandular fever" by Pfeiffer [19] and that of infectious mononucleosis by Sprunt and Evans [20] and for a short period subsequently, pharyngeal infections with lymphocytosis were frequently noted. The term lymphatic reaction was

19. Pfeiffer, E.: Drüsenfieber, Jahrb. f. Kinderh. **29**:257, 1889.

20. Sprunt, T. P., and Evans, F. A.: Mononuclear Leucocytosis in Reaction to Acute Infections ("Infectious Mononucleosis"), Bull. Johns Hopkins Hosp. **31**: 410 (Nov.) 1920.

introduced by Türk [21] to describe the unexplained appearance of lymphocytosis in infections which usually produce neutrophilic leukocytosis. Considerable attention was also directed toward explaining lymphocytosis on the basis of a constitutional lymphatic tendency existing in some persons. Careful scrutiny of the case reports reveals that in many cases the disease was undoubtedly infectious mononucleosis, while in others the disorder was one of the forms of lymphocytosis described in this paper.

Until recently infectious mononucleosis was regarded as a specific disease, with well defined clinical and hematologic features. Sprunt,[22] for instance, included among the obligate features of infectious mononucleosis a febrile course, enlargement of the superficial lymph nodes and the occurrence of a characteristic blood picture. These manifestations could vary in degree and in the order of their appearance. In recent years, however, the diagnosis of infectious mononucleosis has been made in the absence of such cardinal features as fever and lymphadenopathy and greater reliance has been placed on the blood picture. The growing tendency to emphasize the blood picture was expressed in a recent review of infectious mononucleosis,[10] in which this disease was characterized as a "generalized infection whose only essential sign is, at some time in its course, an increase in the mononuclear elements of the blood." The difficulties of such a definition arise in the cases of children, in whom, as already mentioned, lymphocytosis characterizes the blood picture in many infections.

After the introduction of the Paul-Bunnell test, the serum of persons with all sorts of unexplained lymphocytic reactions was tested for heterophile antibody. It was soon found that patients might show the clinical and hematologic features of infectious mononucleosis and yet have a negative reaction to the serologic test and that this discrepancy occurred particularly in the cases of children. On the other hand, it was also observed that positive reactions to the test occurred in cases in which there was an unequivocal blood picture but no enlargement of the lymph nodes and the spleen, or, in other words, in cases with a minimum of the clinical features heretofore regarded as pathognomonic of this disease. With the growing emphasis on the blood picture rather than on the physical signs and with the knowledge that a negative reaction to the Paul-Bunnell test did not preclude a diagnosis of infectious mononucleosis, diverse lymphocytic blood pictures difficult to classify have been placed in this category. This tendency applies at present par-

21. Türk, W.: Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. in Wien **8**:89, 1909.

22. Sprunt, T. P.: Infectious Mononucleosis (Glandular Fever), Internat. Clin. **3**:92 (Sept.) 1933.

ticularly to disorders of infants and young children, in whom this type of blood response is not uncommon. Some of the cases of patients in this age period in which the disorder was regarded as infectious mononucleosis with a negative serologic reaction undoubtedly represent instances of chronic infectious lymphocytosis of the type described in this paper.

It cannot be denied that infectious mononucleosis is a specific disease, with distinctive clinical features present in a greater or less degree, which is associated with a characteristic outpouring of abnormal lymphocytes. Without minimizing the importance of the blood reaction, there are certain signs and symptoms which nevertheless contribute to the diagnosis of this disease. In addition to the fever and lymphadenopathy, which may on occasion be slight, sore throat, splenomegaly, a variety of cutaneous eruptions and a temporary falsely positive reaction to the Kahn and Wassermann tests [23] have characterized the disease in many cases.

The Paul-Bunnell test, on the other hand, requires more extensive application, and its nature needs to be more thoroughly investigated. A wider experience is necessary to determine the lower limit of heterophilic antibody titer which is diagnostic for infectious mononucleosis both before and after absorption tests. The relation of the antibody titer to the age of the patient also has to be studied, for, as already indicated, a survey of case reports reveals that the greatest difficulty with this test is encountered with children. In 4 of the 5 cases of Bernstein,[10] for instance, in which there was a negative serologic reaction the patient was 11 years old or younger.

In view of the abundant evidence that infectious mononucleosis represents a specific symptom complex, the two types of infectious lymphocytosis described in this paper may be clearly differentiated from it. It cannot be denied, however, that a sharp separation between infectious lymphocytosis and borderline or mild infectious mononucleosis cannot always be made, because of overlapping in the clinical and hematologic features. The chronic form, however, may be separated from the terminal stages of infectious mononucleosis by the persistence of clinical activity in the former as compared with the absence of symptoms in the latter.

In the cases of acute infectious lymphocytosis the stage of maximum leukocytosis was not associated with symptoms or physical signs. Such cases are not unique but may be found in the literature under the caption of infectious mononucleosis. Recently, Reyersbach and Lenert [24] reported a group of such cases from an institution in which 16 children over a

23. Sadusk, J. F., Jr.: The Skin Eruption and False-Positive Wassermann in Infectious Mononucleosis (Glandular Fever), Internat. Clin. **1**:239 (March) 1941.

24. Reyersbach, G., and Lenert, T. F.: Infectious Mononucleosis Without Clinical Signs or Symptoms, Am. J. Dis. Child. **61**:237 (Feb.) 1941.

period of six months showed hyperleukocytosis with a striking increase in lymphocytes. The lymphocytes were of the small normal type, and the abnormal cells of infectious mononucleosis were not found. The result of the Paul-Bunnell test was negative in all cases, and in none was there an elevation of temperature, glandular or splenic enlargement, pharyngitis or rash. The disorder in these cases was regarded as infectious mononucleosis without clinical signs or symptoms. From the criteria already outlined for the two conditions, it seems that a more appropriate category would have been infectious lymphocytosis. Wilson and Cunningham [25] reported the case of a 21 year old patient with benign hyperleukocytosis and lymphocytosis which also seems to have been an example of the acute form of infectious lymphocytosis. Clinically and hematologically the disease in this case was distinguished from infectious mononucleosis. Similarly, cases of a disease resembling the chronic form of infectious lymphocytosis have been reported by Rosenbaum [26] as examples of "lymphocytic fever," and these he differentiated from infectious mononucleosis.

The patients in the 2 cases of the acute form were observed for several months after subsidence of the hyperleukocytosis, and during this period the blood reactions resembled those in the cases of the chronic form. This applied more particularly to case 2 (patient J. G.), in which the lymphocytosis and clinical features corresponded to those in the cases of the chronic form. The acute and chronic types of infectious lymphocytosis resemble each other in various hematologic and clinical aspects, but further studies in additional cases are necessary before their relation to each other can be definitely established.

It is entirely possible that the acute type represents a separate entity and that the subsequent chronic phase resulted from infection with another agent. Age apparently constitutes an important factor in producing the blood response, for it was pointed out with reference to the chronic group that the most characteristic lymphocytosis in terms of absolute numbers occurred in children under 6 years of age and was especially prominent in infants. The blood smears of older children usually showed a relative lymphocytosis. The complaints were similar to those of the younger patients, though less severe, but there existed the same clinical confusion with infectious mononucleosis. The diminishing lymphocytosis with increasing age provides an indication as to the period when this symptom complex becomes infrequent. While chronicity in young children appears evident from the cases reported in this paper, information is still limited as to the duration of the lymphocytic response

25. Wilson, C. P., and Cunningham, R. S.: Consideration of Supravital Method of Studying Blood in Cases of Mononuclear Cell Response, Folia haemat. **38**:14 (March) 1929.

26. Rosenbaum, S.: Febris lymphocytotica, Ann. pædiat. **152**:117, 1938.

and the extent of its fluctuation. In the cases presented the duration of the symptoms was usually under six months, but that more prolonged periods may occur is obvious from case 9, in which the low grade febrile reaction had persisted for four years. It is likely that when the child was younger the blood smear showed an absolute increase in the number of lymphocytes and that by the age of 7½ years this response was less marked and a relative lymphocytosis resulted.

To a limited degree, the data also provide evidence that the lymphocytosis does not depend on a peculiar individual response, the so-called constitutional lymphatic reaction. It will be noted in tables 1 and 2 that in each of the first two hospitalizations in cases 1 and 2 a neutrophilic response followed attacks of acute otitis media and pneumonia, respectively. In case 2 (J. G.) during the phase of chronic lymphocytosis, an attack of bronchitis (Dec. 17, 1940) was similarly associated with a preponderance of polymorphonuclear neutrophils in the blood.

No effort was made to determine the agent responsible for the blood reactions, except by the routine examinations of the bacterial flora in the nasopharynx in a few cases. Since the blood reactions appear to be related to infections of the upper respiratory tract, it is conceivable that the organisms represent secondary invaders and that the primary infective agent is a virus, such as has been found responsible for the common cold and influenza. This hypothesis must remain tentative, however, until such time as specific viruses are recovered and corresponding immunologic responses are observed.

As with most disorders, appropriate nomenclature is difficult, and this applies as well to the disease in the cases under discussion. The term infectious lymphocytosis seems to describe the disease in the two groups of cases and to separate it from infectious mononucleosis. In cases of the latter disease, the difficulty of classifying the atypical cells beyond their designation as "mononuclears" without the aid of accessory staining technics is apparent from the varied interpretation given to them by different observers. The term infectious mononucleosis appears, therefore, still to be amply justified. In infectious lymphocytosis, on the other hand, while a few cells may be large and deeply basophilic, there is never any doubt in classifying either them or the larger group of neighboring cells as well defined lymphocytes.

SUMMARY

Two types of lymphocytic blood reactions are described to which the term infectious lymphocytosis has been applied.

In one type, which occurs infrequently, unexpected hyperleukocytosis with absolute and relative lymphocytosis appears for a short period and is not accompanied by any recognizable symptoms or physical signs. In

the 2 cases of this type reported in this paper the maximum white cell counts were 44,300 and 98,000 cells per cubic millimeter respectively.

The second type is frequently encountered in pediatric practice and includes cases in which after an infection of the upper respiratory tract low grade fever continues to be present for prolonged periods. Associated symptoms include anorexia, pallor, fatigability and paraumbilical pain. The blood in such cases shows a lymphocytic preponderance instead of the expected neutrophilic response and moderate leukocytosis. This symptom complex occurs most characteristically in infants and in young children.

Examination of bone marrow in 3 cases showed an increase in lymphocytes as the only abnormality.

These two types are classified as acute and chronic infectious lymphocytosis, respectively, and are differentiated clinically, hematologically and serologically from infectious mononucleosis, leukemia and miscellaneous infections associated with lymphocytosis.

It is pointed out that many lymphocytic blood responses in children whose titer of heterophilic antibody is normal belong in the class of infectious lymphocytosis rather than infectious mononucleosis.

Acute and chronic infectious lymphocytosis may represent separate entities, although there is some evidence that they may be related.

The etiologic agent of each type is probably not represented by the bacterial flora obtained from the nasopharynx but probably is an as yet undetermined virus related to infection of the upper respiratory tract.

The prognosis in both types of infectious lymphocytosis is favorable. Treatment of the chronic type is symptomatic and should be directed toward relieving nasopharyngeal infection.

Miss Elbée Bynum made the drawings.

STUDIES OF BLOOD OF HIGH SCHOOL GIRLS

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The scarcity of information concerning the normal blood picture during adolescence suggested the feasibility of investigating in a large group of healthy high school girls some factors of physiologic significance. Accordingly, determinations of the hemoglobin content, the red cell count, the white cell count, the percentage of reticulocytes and the red cell diameter were made on 258 high school girls ranging in age from 12 to 19 years, 98 per cent of whom were between the ages of 13 and 18 years. This group represented a random sampling of high school girls from several Minnesota communities.[1] The subjects were selected with the aid of the school nurse or some other member of the staff who was familiar with their physical status.

METHODS

Samples of blood were obtained from freely flowing drops secured by puncture of the finger tip. Determinations of the hemoglobin content were made in duplicate or triplicate by the Newcomer method. The disk had been standardized by the oxygen capacity method. Red cell and white cell counts were each made on two separate dilutions of blood; Thoma automatic pipets, certified by the United States Bureau of Standards, were used. For the estimation of the percentage of reticulocytes a film of an alcoholic solution of brilliant cresyl blue was spread on several clean slides and allowed to dry. Duplicate preparations were made by smearing a thin blood film over the stain and incubating in a moist chamber. Five hundred red cells were counted on each slide and the mean percentage of reticulated cells calculated therefrom.

Cell diameters were determined by measuring 100 cells on each of two dry stained films for each subject. The drop of blood was spread lengthwise on the

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1. Cooperation in the conduct of this study was given by the superintendents, the members of the staffs and the students of the high schools in Ada, Barnesville, Benson, Granite Falls, Buhl, Coleraine, Eveleth and Mountain Iron, Minn., and at the Wilson High School, St. Paul.

slide in one instance and crosswise in the other, to compensate for any influence of the mechanics of spreading on the shape of the cell. However, a comparison of means indicated that no mechanical alteration in the shape of the cells occurred. One diameter of all normal cells in a field was measured, with a calibrated Bausch & Lomb filar micrometer.

Precautions were taken to reduce to a minimum those variables which would influence the results of this study. Determinations were carried out by the same investigators, and all observations were made early in the fall to eliminate possible seasonal differences in the hemoglobin level, such as have been reported by Platt and Freeman [2] and Ingersoll.[3]

Several workers have reported evidences of diurnal variation in hemoglobin content and cell counts. After observing 4 healthy young men Ward [4] reported a fluctuation in red cell counts of 5 per cent within a day, the relatively high values being obtained in the morning and the lower ones in the afternoon. Smith and Prest,[5] however, observed no significant diurnal variations either in the red cell count or in the total hemoglobin content. McCarthy and Van Slyke [6] noted no consistent alteration in hemoglobin levels with the time of day. Although they reported that the hemoglobin content was usually lower in the evening than in the morning, the blood of subjects showing such decreases on one day frequently showed the opposite tendency on the next.

In the present study it seemed advisable to ascertain whether the results of examination on blood secured in the morning and in the afternoon were comparable. The means of 104 red cell counts made in the morning and of 99 counts made in the afternoon were 4,170,000 and 4,100,000, respectively, per cubic millimeter. The difference between these means, 70,000, was of low statistical significance ($p = 0.0278$). The data used for this comparison were those secured in communities in which observations were made both in the morning and in the afternoon. Comparable values for hemoglobin content in this same series were 12.21 and 12.17 Gm. per hundred cubic centimeters, and those for the proportions of reticulocytes were 1.16 and 1.12 per cent. Although the values for the observations made in the morning were on the average slightly higher than those for the investigations carried out in the afternoon, the differences were not of statistical significance.

RESULTS

Variation with Age.—In table 1 the mean values, the standard deviations and the coefficients of variation for the hemoglobin content, the red cell count, the white cell count, the percentage of reticulocytes and the red cell diameter for the 258 healthy high school girls used in this study are arranged according to age.

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2. Platt, V. E., and Freeman, R. G.: Seasonal Variation in Hemoglobin, Proc. Soc. Exper. Biol. & Med. **27**:687, 1930.

3. Ingersoll, W.: Hemoglobin Values in Normal Adults Over a Period of Time, J. Lab. & Clin. Med. **21**:787, 1936.

4. Ward, H. C.: The Hourly Variations in the Quality of Hemoglobin and in the Number of Corpuscles in Human Blood, Am. J. Physiol. **11**:394, 1904.

5. Smith, C., and Prest, M.: Further Observations on the Normal Variations in Erythrocyte Values in Women, Am. J. Physiol. **99**:562, 1932.

6. McCarthy, E. F., and Van Slyke, D. D.: Diurnal Variations of Hemoglobin in the Blood of Normal Men, J. Biol. Chem. **128**:567, 1939.

It may be observed that the mean hemoglobin value for the 12 to 13 year old group was 12.56 ± 0.93 Gm.[7] per hundred cubic centimeters of blood. In the 14 year old group, the hemoglobin level shows a statistically significant decrease to 12.05 ± 0.74 Gm. ($p = > 0.0069$). The hemoglobin value remained at essentially the same low level in the next three age groups (15 to 17 years), but in the 18 to 19 year old group it had risen to the level of the 12 to 13 year old group. The mean for all ages studied was 12.21 ± 0.80 Gm. per hundred cubic centimeters of blood.

TABLE 1.—*Blood Values for Healthy High School Girls*

Age, years	12-13	14	15	16	17	18-19	All Ages
Number of subjects	36	43	53	60	48	18	258
Hemoglobin, Gm. per 100 cc. of blood							
Mean value	12.56	12.05	12.15	12.15	12.08	12.58	12.21
Standard error	± 0.93	± 0.74	± 0.86	± 0.75	± 0.76	± 1.00	± 0.80
Coefficient of variation, per cent	7.40	6.14	7.08	6.17	6.29	7.95	6.55
Red cell count, millions per cu. mm. of blood							
Mean value	4.22	4.20	4.13	4.09	4.13	4.14	4.15
Standard error	± 0.24	± 0.24	± 0.23	± 0.25	± 0.24	± 0.23	± 0.24
Coefficient of variation, per cent	5.69	5.71	5.57	6.11	5.81	5.56	5.78
Reticulocytes, per cent							
Mean value	1.20	1.23	1.07	1.00	1.02	1.01	1.08
Standard error	± 0.60	± 0.71	± 0.71	± 0.64	± 0.58	± 0.40	± 0.65
Coefficient of variation, per cent	50.00	57.72	66.36	64.00	56.86	39.60	60.18
White cell count, thousands per cu. mm. of blood							
Mean value	6.70	7.89	7.30	7.12	7.53	7.60	7.34
Standard error	± 1.45	± 1.87	± 1.84	± 1.61	± 1.79	± 1.82	± 1.77
Coefficient of variation, per cent	21.64	23.70	25.20	22.61	23.77	23.95	24.11
Red cell diameter, microns							
Number of subjects	14	27	31	37	24	12	145
Mean value	7.84	7.82	7.93	7.95	7.89	7.94	7.90
Standard error	± 0.19	± 0.20	± 0.20	± 0.17	± 0.20	± 0.17	± 0.20
Coefficient of variation, per cent	2.42	2.56	2.52	2.14	2.53	2.14	2.53

A comparison of the results of the present study with those reported by Mugrage and Andresen [8] for a similar age group indicates that these workers secured appreciably higher values. They observed 10 girls in each age group from 13 to 21 years and secured values for the hemoglobin content of the blood ranging from 14.42 ± 0.77 Gm. per hundred cubic centimeters for the 12 to 13 year old group to 14.79 ± 0.83 Gm. for the 15 to 17 year old group, with a decrease of 14.54 ± 0.79 Gm. for the 19 to 21 year old group. Since all of the subjects of their study lived in Denver or its vicinity, it is possible that the hemoglobin levels were influenced by the altitude.

7. Standard error is used throughout this paper.

8. Mugrage, E. R., and Andresen, M. I.: Red Blood Cell Values in Adolescence, Am. J. Dis. Child. **56**:997 (Nov.) 1938.

Hemoglobin levels comparable to those obtained in the present study were reported by Osgood and Baker [9] for children residing in Portland, Ore. Their mean value for the 12 year old group was 12.0 Gm. per hundred cubic centimeters and for the 13 year old group 12.92 Gm. Osgood [10] determined the hemoglobin levels of 152 females, ranging in age from 14 to 30 years, and secured a mean value of 13.91 Gm. per hundred cubic centimeters of blood, with a range of 11.5 to 16.0 Gm. The mean hemoglobin values reported by Williamson [11] for girls aged 11 to 15 years and 16 to 20 years were 14.87 and 15.64 Gm., respectively. However, he suggested that the values obtained in his study might be relatively high.

The low hemoglobin levels observed in the present study for girls 14 to 17 years old may be attributable in part to the rapid body development of this period. The acceleration in the rate of growth has been reported to start one to two years before the date of the first menstruation, reaching its maximum around the thirteenth year and then declining to the end of the growth period (Roberts [12]).

Determinations of the red cell count gave a mean value for the 12 to 13 year old group of 4,220,000 ± 240,000 cells per cubic millimeter of blood. A gradual decrease was noted with age, similar to that observed for the hemoglobin content, the count reaching a low point, for the 16 year old group, of 4,090,000 ± 250,000, a statistically significant decrease from the value for the 12 to 13 year old group ($p = > 0.0124$). This was followed by a slight increase to 4,140,000 ± 230,000 for the 18 to 19 year old group. The mean value for all ages studied was 4,150,000 ± 240,000 cells per cubic millimeter of blood.

Mugrage and Andresen reported appreciably higher red cell counts than those obtained in the present study. Their range for this age group was from 4,660,000 ± 200,000 for the 12 to 13 year old group to 4,690,000 ± 220,000 for the 15 to 17 year old group. Osgood and Baker reported mean red cell counts of 5,040,000 for 12 year old girls and 5,130,000 for 13 year old girls, while Osgood recorded a mean value of 4,830,000, with a range of 4,200,000 to 5,400,000, for his subjects.

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9. Osgood, E. E., and Baker, R. L.: Erythrocyte, Hemoglobin, Cell Volume and Color, Volume and Saturation Index Standards for Normal Children of School Age, Am. J. Dis. Child. **50**:343 (Aug.) 1935.

10. Osgood, E. E.: Normal Hematologic Standards, Arch. Int. Med. **56**: 849 (Nov.) 1935.

11. Williamson, C. S.: Influence of Age and Sex on Hemoglobin: A Spectrophotometric Analysis of Nine Hundred and Nineteen Cases, Arch. Int. Med. **18**:505 (Oct.) 1916.

12. Roberts, L. J.: Nutrition Work with Children, ed. 2, Chicago, University of Chicago Press, 1935.

The relatively wide individual differences in the percentage of reticulocytes are indicated by the high coefficients of variation (table 1). The mean values for the reticulocyte counts for the various age groups were 1.00 or above. Osgood reported a range for the proportion of reticulocytes of 0.50 to 3.00 per cent, with a mean of 1.46, for males and females 4 to 30 years of age.

Wide individual differences in white cell counts, also, in each age group are shown by the relatively high coefficients of variation. No evidence was secured of the influence of age on the level of the white cell count; the lowest mean, 6,700 ± 1,450 cells per cubic millimeter, was secured for the 12 to 13 year old group, and the highest mean, 7,890 ± 1,870, was obtained for the 14 year old group. The mean value for all ages was 7,340 ± 1,770 cells per cubic millimeter of blood. Osgood and his co-workers [13] reported that the total leukocyte counts for 46 girls 15 to 18 years of age ranged from 4,000 to 13,500, with a mean of 8,160, while Osgood in an earlier study had cited a mean value of 8,300, with a range of 4,500 to 13,500, for the leukocyte counts for boys and girls 8 to 18 years of age. These mean values are slightly higher than those obtained in the present study.

The mean red cell diameter for all age groups studied was 7.90 ± 0.20 microns. The data secured suggest a slight change in cell diameter with age, since the mean diameter for the 12 to 13 year old group, 7.84 ± 0.19 microns, increased to 7.95 ± 0.17 microns for girls 16 years of age. The difference, when tested statistically, showed low significance ($p = > 0.0455$). In an earlier study [14] we had noted a similar tendency in the values for healthy young college women. This observation, however, is not in accordance with the results of Fischer,[15] who reported that age did not influence cell diameter.

Variation with Menstruation.—It has been suggested that, in addition to the effect of growth, losses of blood through menstruation may contribute to the frequency with which anemia occurs in adolescent girls. In order to ascertain whether the results of the present investigation would give evidence of such an effect, a comparison was made of the blood values obtained for girls in whom the menstrual function had been established with those for girls in the same age group in whom it had

13. Osgood, E. E.; Baker, R. L.; Brownlee, I. E.; Osgood, M. W.; Ellis, D. M., and Cohen, W.: Total, Differential, and Absolute Leukocyte Counts and Sedimentation Rates of Healthy Adolescents Fifteen to Eighteen Years of Age, J. Lab. & Clin. Med. **24**:905, 1939.

14. Donelson, E. G.; Leichsenring, J. M., and Wall, L. M.: The Diameter of Red Blood Cells in Healthy Young Women, Am. J. Physiol. **128**:382, 1940.

15. Fischer, H.: Untersuchungen über den Durchmesser der roten Blutkörperchen im Kindesalter, Monatschr. f. Kinderh. **63**:194, 1935.

not been established. It may be noted from table 2 that essentially identical values were secured for the hemoglobin content, the red cell count and the red cell diameter for the girls in the 12 to 13 year old group who had passed the menarche and for those who had not. Since the girls who had menstruated had so recently passed the menarche, it was not to be expected that the periodic losses of blood could have altered the blood picture appreciably. In the case of the 14 and 15 year old girls who had not passed the menarche and the 14 year old girls who had, however, the mean values for both the hemoglobin content and the red cell count were higher for the former than for the latter. The difference in the hemoglobin values (0.65 Gm. per hundred cubic centimeters of blood) proved to be statistically significant ($p = < 0.0124$).

To test further the effect of menstruation on the hemoglobin level, the 14 year old group was divided into two classes: those in whom

TABLE 2.—*Effect of Establishment of the Menstrual Function on Blood Values*

	Age, Years	Number	Mean Hemoglobin Content, Gm. per 100 Cc. of Blood	Mean Red Cell Count, Millions per Cu. Mm. of Blood	Red Cell Diameter, Microns	
					Number of Subjects	Mean Value
Girls who had not menstruated	12-13	22	12.55	4.22	10	7.84
Girls who had menstruated.....	13	14	12.58	4.23	5	7.87
Girls who had not menstruated	14-15*	13	12.56	4.27	10	7.88
Girls who had menstruated.....	14	33	11.91	4.18	20	7.81

* Three 15 year old girls were included in this group.

menstruation had been established for less than two years and those in whom it had been established for two or more years. It was found that the mean hemoglobin value for the former class was 12.03 Gm. per hundred cubic centimeters of blood, while for the latter it was 11.83 Gm. The difference was statistically significant ($p = < 0.0164$). Although these results suggest that the menstrual blood losses contribute to the lowering of the hemoglobin level, it must be recognized that since no data on growth were secured for these subjects the difference in hemoglobin levels may be due to the particular phase of the accelerated growth period in which the groups fall. On the other hand, it will be recalled that no differences were observed in the blood values for the 12 and 13 year old girls who had passed the menarche and for those who had not, and an influence of growth might be anticipated in these groups also.

Since the data indicate that menstruation influenced the hemoglobin level, table 3 was prepared with a view to determining the effect on the

blood picture of the number of years elapsed since the onset of menstruation. In the group of girls studied the mean age at which the menstrual flow was established was 12.9 ± 1.1 years. It is apparent from table 3 that the lowest mean values for hemoglobin were secured for those groups of girls in whom menstruation had been established for two and three years and that higher values were obtained for the groups in whom it had been established four, five and six years. The red cell count tended to follow the hemoglobin level. Since the higher values were observed for the groups of girls who had menstruated for longer periods and who might be presumed to be approaching the end of their growth periods, it seems that growth influenced the blood picture to a greater extent than did the years of menstruation. The decrease in the

TABLE 3.—*Effect on Blood Values of the Number of Years Elapsed Since Onset of Menstruation*

Years of Menstruation	Number of Subjects	Mean Hemoglobin Content, Gm. per 100 Cc. of Blood	Mean Red Cell Count, Millions per Cu. Mm. of Blood	Percentage of Reticulocytes		Red Cell Diameter, Microns	
				Number of Subjects	Mean Value	Number of Subjects	Mean Value
<1	42*	12.54	4.24	42	1.23	23	7.87
1	34	12.20	4.17	33	1.14	19	7.87
2	59	12.02	4.10	58	1.07	32	7.91
3	64	12.02	4.12	62	1.04	34	7.90
4	33	12.36	4.13	31	1.14	21	7.94
5	19	12.34	4.15	19	0.91	13	7.90
6	6	12.48	4.24	6	0.75	3	7.86

* Includes 35 subjects who had not passed the menarche.

percentage of reticulocytes with increasing years of menstruation suggests a gradual diminution in erythropoietic stimulation. The data on the diameter of the red cells do not indicate any influence of the number of years of menstruation on cell size other than that which has already been noted in table 1 in connection with the effect of age.

In the group of subjects studied the length of the menstrual period ranged from 2 to 7 days, with a mean of 4.6 ± 1.2 days. This is in agreement with the data on the duration of flow given by McCance, Luff and Widdowson,[16] who reported a mean value of 4.5 days for a group of 167 normal women. Barer and Fowler[17] found that the amount of blood lost tended to increase with the length of the menstrual period. In table 4 the data secured in the current study are arranged

16. McCance, R. A.; Luff, M. C., and Widdowson, E. L.: Physical and Emotional Periodicity in Women, J. Hyg. **37**:571, 1937.

17. Barer, A. P., and Fowler, W. M.: The Blood Loss During Normal Menstruation, Am. J. Obst. & Gynec. **31**:979, 1936.

according to the mean length of the menstrual period. In general, age did not influence the duration of flow, since in each classification the mean age was between 15 and 16 years, with the exception of 3 subjects who reported a 2 day menstrual period, whose mean age was slightly less than 15 years. Although the hemoglobin values for the groups with menstrual periods of 5, 6 and 7 days were somewhat lower than those for the groups having shorter periods, with the exception of the 3 subjects whose periods averaged 2 days in length, the difference was not significant ($p = > 0.0891$). Somewhat higher red cell counts were noted for the groups with 2 and 3 day menstrual periods than for those with longer periods, but no consistent influence of the length of the period was manifested. Mean values for cell diameter were remarkably uniform for the groups reporting 2, 3, 4 and 5 day menstrual periods. Although somewhat smaller diameters were obtained for the subjects

TABLE 4.—*Effect of the Length of the Menstrual Period on Blood Values*

Length of Menstrual Period, Days	Number of Subjects	Mean Age, Years	Mean Hemoglobin Content, Gm. per 100 Cc. of Blood	Mean Red Cell Count, Millions per Cu. Mm. of Blood	Red Cell Diameter, Microns	
					Number of Subjects	Mean Value
2	3	14.7	11.68	4.21	2	7.93
3	35	15.8	12.23	4.26	17	7.93
4	73	15.9	12.28	4.14	46	7.94
5	70	15.5	12.15	4.18	41	7.90
6	25	15.8	11.78	4.15	9	7.75
7	17	15.2	12.07	4.16	10	7.85

who had 6 and 7 day periods, no significance can be attached to these differences because of the relatively limited number of girls in these two groups.

As a further inquiry into the effect of menstruation on the blood picture of adolescent girls, the various factors studied were arranged on the basis of phases in the menstrual cycle. The intermenstrual phase was divided into four five day periods and a fifth period which included the twenty-first and all subsequent days after menstruation, as indicated in table 5. It may be observed that the hemoglobin values tended to vary with the cycle, being relatively high during menstruation and the first postmenstrual period, decreasing thereafter during the second, third and fourth postmenstrual periods but returning in the final postmenstrual period to a level slightly above that observed during menstruation. The values for the red cell count tended to follow those for the hemoglobin content, except that the lowest value was observed during the menstrual period. The values for the percentage of reticulo-

cytes followed a curve which was the reverse of that for the hemoglobin values, those during menstruation and the first postmenstrual period being relatively low and those during the second, third and fourth postmenstrual periods somewhat higher, with a tendency to decrease toward the menstrual level in the final postmenstrual period.

The mean values for the white cell count showed great uniformity throughout the various periods in the menstrual cycle except that a considerably lower mean value was secured during the second postmenstrual period. The mean values for the red cell diameter were not influenced by the various periods of the menstrual cycle.

TABLE 5.—*Effect of the Period in the Menstrual Cycle on Blood Values*

	Menstruation	Periods in the Menstrual Cycle				
		1	2	3	4	5
Days after menstruation	..	1-5	6-10	11-15	16-20	21 and Over
Number of subjects	23	37	31	45	37	47
Mean age, years	16.0	15.5	15.3	16.0	15.6	15.7
Hemoglobin content, Gm. per 100 cc. of blood						
Mean value	12.19	12.21	12.11	12.09	12.07	12.26
Standard error	± 0.73	± 1.04	± 0.72	± 1.00	± 0.78	± 0.67
Red cell count, millions per cu. mm. of blood						
Mean value	4.04	4.18	4.14	4.11	4.13	4.18
Standard error	± 0.18	± 0.26	± 0.24	± 0.23	± 0.22	± 0.22
Percentage of reticulocytes						
Mean value	0.95	0.90	1.12	1.09	1.12	1.03
Standard error	± 0.49	± 0.63	± 0.72	± 0.66	± 0.76	± 0.54
White cell count, thousands per cu. mm. of blood						
Mean value	7.76	7.62	6.55	7.42	7.55	7.55
Standard error	± 1.84	± 1.94	± 1.28	± 1.50	± 1.91	± 1.95
Red cell diameter, microns						
Number of subjects	17	23	20	26	17	20
Mean value	7.92	7.89	7.90	7.89	7.92	7.91
Standard error	± 0.21	± 0.22	± 0.18	± 0.19	± 0.15	± 0.20

Blood values reported by a number of workers for relatively limited numbers of subjects, on some of whom daily and on others periodic observations were made throughout several menstrual cycles, did not suggest that menstruation exercised a consistent effect on the various factors studied (Smith and McDowell[18]; Reich and Green[19]; Smith,[20]

18. Smith, C., and McDowell, A. M.: Normal Rhythm of White Blood Cells in Women, Arch. Int. Med. **43**:68 (Jan.) 1929.

19. Reich, C., and Green, D.: Red Cell Regeneration During the Menstrual Cycle, Arch. Int. Med. **49**:534 (March) 1932.

20. Smith, C.: Daily Erythrocyte Counts in Menstrual and Intermenstrual Periods, Am. J. Physiol **114**:452, 1936.

and Leverton and Roberts [21]). On the other hand, Rowe and Guagenty [22] and Duckles and Elvehjem [23] observed a downward trend of all factors studied during menstruation and a gradual recovery during the postmenstrual phase. The data obtained in the present study indicate some fluctuation in hemoglobin content, red cell count and percentage of reticulocytes with the periods in the menstrual cycle.

SUMMARY

Studies on the blood of 258 normal high school girls, ranging in age from 12 to 19 years, gave the following mean values: hemoglobin content, 12.21 ± 0.80 Gm.; red cell count, 4,150,000 ± 240,000 cells per cubic millimeter; white cell count, 7,340 ± 1,770 cells per cubic millimeter; proportion of reticulocytes, 1.08 ± 0.65 per cent, and diameter of red cells, 7.90 ± 0.20 microns.

The mean values for hemoglobin content were lower for the 14, 15, 16 and 17 year old groups than for the 12 to 13 year old group but rose to those of the 12 to 13 year old level in the 18 year old group. Values for the red cell count tended to follow those for hemoglobin content. The mean percentage of reticulocytes showed a gradual decrease with age, whereas the mean red cell diameter showed a slight increase. The mean values for the white cell count were not influenced by the age of the subjects.

Comparison of the hemoglobin values and the red cell counts for girls who had not experienced the menarche with those for girls in the same age group in whom the menstrual function had been established demonstrated the lowering effect of the periodic loss of blood on the hemoglobin level for the girls in the 14 to 15 year old group but not for those in the 12 to 13 year old group.

Of the two factors which may affect hemoglobin values and red cell counts in adolescent girls, that is, the rate of growth and the periodic loss of blood, the data suggest that the former exerts the greater influence on the blood picture.

The mean age of establishment of the menstrual function was observed to be 12.9 ± 1.1 years, and the mean length of the menstrual flow was 4.6 ± 1.2 days.

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21. Leverton, R. M., and Roberts, L. J.: Hemoglobin and Red Cell Content of the Blood of Normal Women During Successive Menstrual Cycles, J. A. M. A. **106**:1459 (April 26) 1936.

22. Rowe, A. W., and Guagenty, M. C.: A Note on the Menstrual Influence on Blood Morphology, J. Lab. & Clin. Med. **20**:253, 1934.

23. Duckles, D., and Elvehjem, C. A.: Hemoglobin Studies on College Women with Special Reference to the Effect of Menstruation, J. Lab. & Clin. Med. **22**: 607, 1937.

Although for girls who had the longer menstrual periods (five, six and seven days) the values both for hemoglobin content and for red cell count were somewhat lower than the corresponding values for girls who had the shorter periods (two, three and four days), no statistically significant difference could be demonstrated.

The hemoglobin values, the red cell counts and the percentages of reticulocytes showed variations with the periods of the menstrual cycle.

The values for the diameter of the red cells and the white cell counts were not influenced by the time elapsed since the menarche, the length of the menstrual flow or the periods of the menstrual cycle.

SERUM PHOSPHATASE AS AN AID IN THE DIAGNOSIS OF CRETINISM AND JUVENILE HYPOTHYROIDISM

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In a previous communication [1] preliminary data were presented which showed that the level of serum phosphatase of children with untreated hypothyroidism tended to be abnormally low and that it was restored to normal by thyroid therapy. Only four other reports on measurements of the serum phosphatase of children with hypothyroidism have been found in the literature.[2] In the present communication are reported observations which show that the phosphatase determination is of clinical value as an aid in the diagnosis of hypothyroidism during infancy and childhood.

MATERIAL AND METHODS

A total of 30 infants and children with hypothyroidism have been studied. The level of phosphatase in the serum was determined for 12 patients before thyroid was given and for 28 patients after thyroid therapy. The values for serum phosphatase for the latter group represent the averages of the measurements obtained during periods when the clinical response to therapy appeared to be satisfactory. The children with hypothyroidism ranged in age from 3 months to 12 years.

To provide control data, the level of serum phosphatase was determined for a group of 70 normal children who were being observed periodically at the Center

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From the Infants' and the Children's Hospitals and the Department of Pediatrics, Harvard Medical School, and the Department of Child Hygiene, Harvard School of Public Health.

1. Talbot, N. B.: Influence of Thyroid Hormone on Serum Phosphatase, Endocrinology **24**:872, 1939.

2. (*a*) Smith, J.: Plasma Phosphatase in Rickets and Other Disorders of Growth, Arch. Dis. Childhood **8**:215, 1933. (*b*) Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: III. Serum Phosphatase in Diseases of the Bone; Interpretation and Significance, Arch. Int. Med. **54**:88 (July) 1934. (*c*) Morris, N., and Peden, O. D.: Plasma Phosphatase in Disease: A Review, Quart. J. Med. **6**:211, 1937.

for Research in Child Health and Development, Harvard School of Public Health.[3] They were between 2 and 10 years of age and were apparently in good health. In addition, measurements were made for 5 normal infants in the Boston Lying-in Hospital.

The level of phosphatase was determined on freshly obtained serum by a slight modification of the method of Bodansky.[4] The method consists of incubating 0.5 cc. of serum with 5 cc. of a solution containing 0.5 per cent of sodium glycerophosphate and 0.42 per cent of monosodium diethylbarbiturate at 37 C. (98.6 F.) for one hour. The mixture is then cooled in ice water and 4.5 cc. of a 10 per cent trichloroacetic acid solution is added. The precipitated proteins are filtered off, Whatman filter paper no. 42 being used, and the total inorganic phosphorus is determined on 1.0 cc. of the filtrate made up to 10 cc. as follows: 1.0 cc. of the filtrate, 7.6 cc. of distilled water, 1 cc. of 2.5 per cent ammonium molybdate in one-fifth normal sulfuric acid and 0.4 cc. of 0.25 per cent aminoaphtholsulfonic acid reagent (Folin's manual, 5th Edition p. 175, 1934). At the end of fifteen minutes the intensity of the blue color developed is measured in the Evelyn photoelectric colorimeter, filter 660 being used, with the blank solution set at 100 on the galvanometer scale. The result is read off from a calibrated curve.

The values obtained for the normal children and for the children with hypothyroidism before and after treatment are summarized in figure 1. The serum phosphatase, expressed in Bodansky units per hundred cubic centimeters of serum, is indicated by the abscissa. The percentage incidence of each level of phosphatase among the children in each group is represented by the ordinate. It will be seen that the values for serum phosphatase for the normal group range from 4.5 to 12 units.[5] On the other hand, the value for phosphatase was lower than 4.5 units for 11 of the 12 patients with hypothyroidism who had not received desiccated thyroid. However, during the periods when thyroid was being administered to the patients with hypothyroidism, the level of phosphatase was within normal limits.

The effect of thyroid on the level of serum phosphatase of 2 patients with hypothyroidism is shown in more detail in figures 2 and 3. The duration of the observation is represented by the abscissa. The number of grains of thyroid U. S. P. administered daily and the number of

3. Stuart, H. C., and others: The Center for Research in Child Health and Development, School of Public Health, Harvard University: I. The Center, the Group Under Observation, Sources of Information, and Studies in Progress, Monographs of the Society for Research in Child Development, vol. 4, no. 1, Washington, D. C., National Research Council, 1939.

4. Bodansky, A.: Phosphatase Studies: II. Determination of Serum Phosphatase; Factors Influencing the Accuracy of the Determination, J. Biol. Chem. **101**:93, 1933.

5. The average for the entire group was 7.2 units. There was no significant difference between the average value for boys (7.4 units) and that for girls (7.0 units). There was no apparent variation in the values for children between 2 and 10 years of age.

units of phosphatase per hundred cubic centimeters of serum are given by the ordinate. The figures show that the level of phosphatase rose when thyroid was administered and that the values diminished as thyroid therapy was reduced or discontinued.

In the table the values for serum phosphatase for 12 children with hypothyroidism are given with some of the other nonspecific laboratory indexes of thyroid underactivity, namely, the basal metabolic rates, the

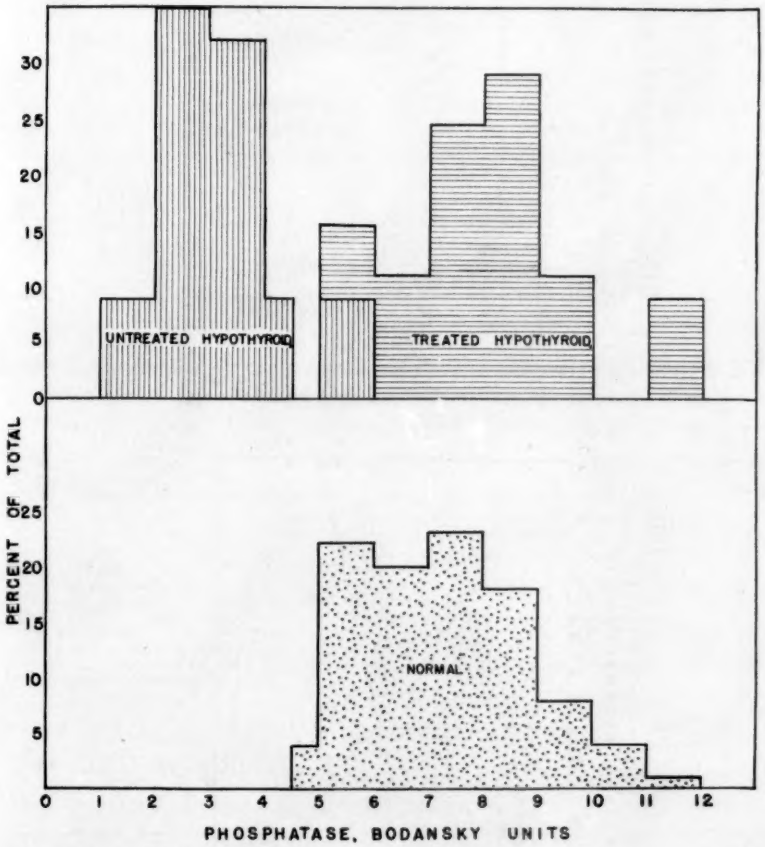

Fig. 1.—The levels of serum phosphatase of normal children and of children with untreated and treated hypothyroidism.

values for serum cholesterol and the degrees of osseous development. In the table those values which by normal standards were suggestive of hypothyroidism are printed in bold face type; the remaining values were within the limits of normal variation. It will be seen that in this series of 12 children with hypothyroidism the level of cholesterol in the plasma was abnormally elevated for 2 of 9 (22 per cent) for whom this measure-

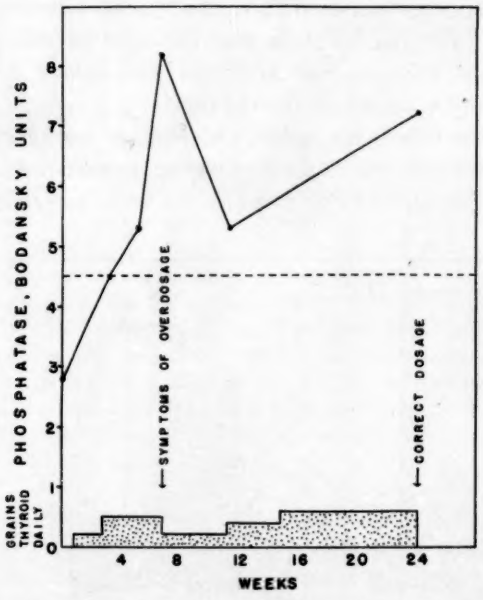

Fig. 2 (case 3).—The effect of the administration and the withdrawal of thyroid on the level of serum phosphatase of a cretin aged 9 months.

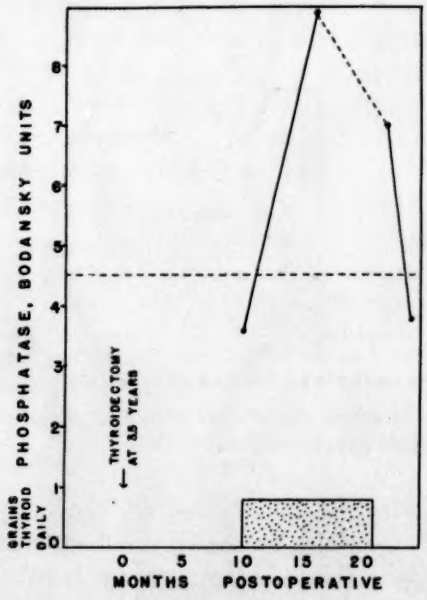

Fig. 3 (case 8).—The effect of the administration and the withdrawal of thyroid on the level of serum phosphatase of a 4 year old girl with hypothyroidism secondary to thyroidectomy for thyroglossal cyst.

ment was obtained and that the basal metabolic rate for 6 of 9 (67 per cent) was abnormally low. These results are essentially in agreement with the recent observations of Wilkins and associates.[6] The observation that the osseous development of 3 of the 12 children (25 per cent) was within normal limits indicates that the accuracy of this index of thyroid deficiency is limited by the fact that time must elapse after the onset of thyroid deficiency before retardation in osseous development becomes evident. In contrast to the foregoing observations, the phosphatase values were abnormally low for 11 of the 12 children with hypothyroidism, or for over 90 per cent.

Level of Serum Phosphatase and Other Laboratory Indexes of Hypothyroidism for Twelve Children with Untreated Hypothyroidism

Case No.	Diagnosis	Chronologic Age, Years	Skeletal Age,* Years	Basal Metabolic Rate,† per Cent	Plasma Cholesterol,‡ Mg. per 100 Cc.	Serum Phosphatase, Bodansky Units
1	Cretinism	3 mo.	3 mo.	—23	90	3.3
2	Cretinism	6 mo.	3 mo.	....	..	2.7
3	Cretinism	9 mo.	3 mo.	—21	97	2.7
4	Cretinism	10 mo.	Birth	—16	94	4.3
5	Cretinism	1¼	Birth	....	117	1.3
6	Cretinism	1½	6 mo.	—13	112	3.8
7	Juvenile hypothyroidism	3½	1	—30	184	2.7
8	Juvenile hypothyroidism following thyroidectomy at 3½ years of age	4 yr. 2 mo.	4	— 3	469	3.5
9	Juvenile hypothyroidism	5	2	....	...	3.7
10	Cretinism	5 yr. 7 mo.	1½	—23	284	2.9
11	Cretinism	10	4	—42	145	2.2
12	Juvenile hypothyroidism	10	5½	—20	...	5.3

* The skeletal age was estimated by comparing roentgenograms of the wrists with the normal standards of Todd (Atlas of Skeletal Maturation: The Hand, St. Louis, C. V. Mosby Company, 1937). Dr. G. Wyatt made these estimations.

† The basal metabolic rate was estimated by referring to the standard of calories for weight of Talbot (Basal Metabolism Standards for Children, Am. J. Dis. Child. 55:455 [March] 1938). Values below —19 per cent are considered definitely abnormal.

‡ The plasma cholesterol was determined by a slight modification of the method of Bloor, Pelkan and Allen (Determination of Fatty Acids [and Cholesterol] in Small Amounts of Blood Plasma, J. Biol. Chem. 53:191, 1922). Values above 200 mg. per hundred cubic centimeters are considered abnormally high.

COMMENT

The normal values for serum phosphatase for children 2 to 10 years old reported here are in close agreement with those of Bodansky and Jaffe,[2b] who reported that the average normal value for children 5 to 14 years of age is approximately 7 units (range 5 to 14 units) per hundred cubic centimeters of serum. The results of a number of studies[7] have been reported which show that the level of phosphatase

6. Wilkins, L.; Fleischmann, W., and Block, W.: Hypothyroidism in Childhood: I. Basal Metabolic Rate, Serum Cholesterol and Urinary Creatine Before Treatment, J. Clin. Endocrinol. **1**:1, 1941.

7. Kay, H. D.: Phosphatase in Growth and Disease of Bone, Physiol. Rev. **12**:384, 1932. Stearns, G., and Warweg, E.: Studies of Phosphorus of Blood:

(Footnote continued on next page)

in the plasma or serum is definitely higher in children than in normal adults. Barnes and Munks [8] have shown that the level of phosphatase is probably highest during the fourth or fifth month of life. These observations suggest that the lower limit of normal determined in the present study on children for the most part over 2 years old represents a conservative estimate of the lower limit of normal for children under 2 years of age.

The data for this series of children with hypothyroidism indicate that the level of phosphatase in the serum tends to be depressed below normal limits in infants and children with untreated hypothyroidism and that since the depressed, or low, level of phosphatase is raised by the administration of thyroid it is referable to thyroid deficiency. A survey of the literature and a review of the measurements of phosphatase made in the Children's Hospital during the past three years reveal that with the possible exception of certain cases of idiopathic dwarfism a lowered level of phosphatase is not observed in disease [9] which might be confused easily with juvenile hypothyroidism or cretinism. The available evidence [10] indicates that the level of phosphatase is normal in cases of mongolism, a disease often mistaken for cretinism. Thus, the value for serum phosphatase has been found useful as an index of thyroid function in children provided the other diseases which may cause a lowering of the level of serum phosphatase are excluded.

SUMMARY AND CONCLUSIONS

The level of serum phosphatase of infants and children with untreated hypothyroidism is abnormally low. It is restored to normal by adequate thyroid therapy. It is concluded that the measurement of serum phosphatase provides a simple and reliable index of thyroid deficiency during infancy and childhood.

Mrs. A. Hill gave technical assistance in this study.

I. The Partition of Phosphorus in the Whole Blood and Serum, the Serum Calcium and Plasma Phosphatase from Birth to Maturity, J. Biol. Chem. **102**: 749, 1933. Vermehren, E.: Variationen im Phosphatasegehalt des Plasmas im Anschluss an die verschiedenen Lebensalter, Acta med. Scandinav. **100**:244, 1939. Bodansky and Jaffe.[2b]

8. Barnes, D. J., and Munks, B.: Serum Phosphatase, Calcium and Phosphorus Values in Infancy, Proc. Soc. Exper. Biol. & Med. **44**:327, 1940.

9. In certain cases of scurvy, severe malnutrition, severe anemia, arthritis, achondroplasia, splenomegaly and abdominal tumors there may be a lowering of the level of phosphatase in the serum. The average value for phosphatase for 8 children with idiopathic dwarfism was 6.6 units (range 4.5 to 9.0 units) per hundred cubic centimeters of serum.

10. Bixby, E. M.: Biochemical Studies in Mongolism, Proc. Am. A. Ment. Deficiency **44**:59, 1939; cited in Further Biochemical Studies in Mongolism, Am. J. Ment. Deficiency **45**:201, 1940.

RELATION OF CALCIUM, PHOSPHORUS AND NITROGEN RETENTION TO GROWTH AND OSSEOUS DEVELOPMENT

A LONG TIME STUDY OF THREE PRESCHOOL BOYS

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The reports on the amount of the three metabolites—calcium, phosphorus and nitrogen—needed by children of a given age have varied, because, it is believed, there were differences in the growth pattern of the children studied, in the degree of saturation of the tissues at the time of the study and in the availability of the metabolites in the materials fed. Furthermore, the retention of calcium and nitrogen is influenced not only by the amount needed but by whether an adequate amount of phosphorus is supplied by the diet. In many of the studies only calcium balances were reported; comparisons, therefore, may not be valid. The problem is further confused by the fact that many of the studies have been of short duration. Continuous balance studies both with children and with adults have indicated that there is considerable variation from period to period; and although this is due in part to unavoidable inaccuracies in fecal marking, fluctuation in the physiologic condition of the subject at the time of the study also may be partially responsible. Minor infections, even though they produce no appreciable rise in temperature, affect the retention of both nitrogen and phosphorus; if the infection continues and becomes more acute, the retention of calcium may be decreased. Subsequently there is an increase in retention, seemingly an attempt to make up for losses during the period of infection.

To make sure how much calcium, phosphorus and nitrogen children of various ages should be given, long-continued studies must be made with well nourished children who are gaining normally, that is, optimally, throughout the period. Presumably, Outhouse and co-workers [1] carried

From the Iowa Child Welfare Research Station, State University of Iowa.

1. Outhouse, J.; Kinsman, G.; Sheldon, D.; Twomey, I.; Smith, J., and Mitchell, H. H.: The Calcium Requirements of Five Pre-School Girls, J. Nutrition **17**:199, 1939.

out such a study with reference to calcium, since the children studied were given liberal feedings of calcium, about 1,800 mg. per day, during a preliminary period of thirteen to fifteen weeks. The fact that the same amount of calcium was retained when smaller amounts of calcium were being ingested as when larger amounts were fed suggests that the tissues were saturated. Evaluation of the diets from the standpoint of their theoretic content of phosphorus and nitrogen indicates that in each case sufficient amounts had been fed.

According to the present conception, the skeletal age of a well nourished child corresponds to his chronologic age as determined by the standards obtained by studies of roentgenograms of the hand and foot. The various standards, however, do not agree. For example, according to the standard of Flory,[2] the skeletal age of preschool children is about one year below that given by the standard of Todd.[3] In preparing the Harvard standard (Vogt and Vickers [4]), the roentgenograms in the highest and the lowest 10 per cent of the scale were discarded and the remainder divided into three categories on the basis of osseous development: the upper group, or ninetieth percentile, which indicates a stage of development reached by only 10 per cent of all the children; the middle group, which indicates a stage of development reached by 50 per cent, and the lower group, or tenth percentile, which indicates the stage which 90 per cent have reached at any given age period. Theoretically, the ninetieth percentile group is composed of the well nourished, or "advanced," children, the middle 50 per cent of the average children and the tenth percentile group of the poorly nourished, or "slow," children. A classification which divides the children of this study into well nourished, inadequately nourished and poorly nourished groups, without proof of the validity of the grouping, is open to question; it ignores the possible influence of the endocrine glands on skeletal development. Nevertheless, such large numbers of children have been studied, that it seems probable that the skeletal development does reflect the nutritional status of the child.

The present report gives the results of a nine month study of the retention of calcium, phosphorus and nitrogen by 3 preschool boys from private homes of the underprivileged level. Two of the boys, J. E. and

2. Flory, C. D.: Osseous Development in the Hand as an Index of Skeletal Development, Monographs of the Society for Research in Child Development, Washington, D. C., National Research Council, 1936, vol. 1, no. 3.

3. Todd, T. W., and others: Atlas of Skeletal Maturation (Hand), St. Louis, C. V. Mosby Company, 1937.

4. Vogt, E. C., and Vickers, V. S.: Osseous Growth and Development, Radiology **31**:441, 1938.

G. E., were brothers. When the study was undertaken it was assumed that these children were normal, since their weights were within 10 per cent of the normal range of weights for heights. Although the 3 children were somewhat below the average height for their respective ages, they appeared to be well nourished. When the first roentgenograms were taken, which indicated that they were skeletally retarded, to a greater or less degree, depending on the standard used for comparison, there seemed to be an opportunity (1) to test a tentative hypothesis arrived at previously to the effect that high retentions of calcium and phosphorus by children of the preschool age are due in part at least to previous depletion and (2) to determine the time required for the tissues of these skeletally retarded children to become saturated with calcium when they were receiving what was believed to be an optimum diet. Later, when the Harvard standards were published, comparisons of the osseous development of these children were made with both the fiftieth percentile and the ninetieth percentile group.

In view of the seemingly retarded development shown by the first roentgenograms, it was anticipated that the calcium retentions during the first part of the study would be high but that as the skeleton became more nearly saturated they would drop, so that at the end of the study the retentions would be in line with the normal values for well nourished children of the preschool age. Furthermore, it was believed, that correlating changes in the roentgenograms with the amount of calcium retained during the various periods of the study would aid in determining the validity of the published standards of osseous development.

METHODS

The 3 preschool boys under observation, J. E., G. E. and F. V., who were 4 years 10½ months, 3 years 3 months and 4 years 9 months old, respectively, at the beginning of the study, were kept under the same controlled conditions described in a previous paper.[5] They were weighed once daily, after voiding and before breakfast. Four measurements of height were made at the same hour at the beginning of each test period and every five days thereafter. In general, roentgenograms (ten for each child) were made at the beginning of each metabolism period. To conserve space, only the first and last are reproduced here (fig. 1).

Each metabolism period consisted of two successive five day collection periods, which reduced the likelihood of inaccuracies of fecal marking possible with shorter single periods. Since the children returned to their homes for a week end every third week and during the Christmas holidays, each ten day collection period was

5. Daniels, A. L.; Hutton, M. K.; Knott, E. M.; Wright, O., and Forman, M.: Calcium and Phosphorus Needs of Preschool Children, J. Nutrition **10**: 373, 1935.

preceded by a six day preliminary period during which they received the weighed diets, so that the possible untoward effects of the less strict home diet might be overcome.

According to present knowledge the diet contained a liberal amount of calcium —from 53 to 76 mg. per kilogram, or from 1.11 to 1.19 Gm. per child, per day. Of this, from 75 to 78 per cent was supplied by a daily intake of 750 Gm. of milk. During the first five months of the study (period 1), with the exception of slight variations in the amount of orange juice and ascorbic acid, the diet was the same from period to period. It was planned to supply 3.5 Gm. of protein per kilogram, but analysis showed that it contained slightly less than that, namely, 3.4 Gm. Milk, eggs and meat furnished 80 per cent of the protein. The diet supplied from

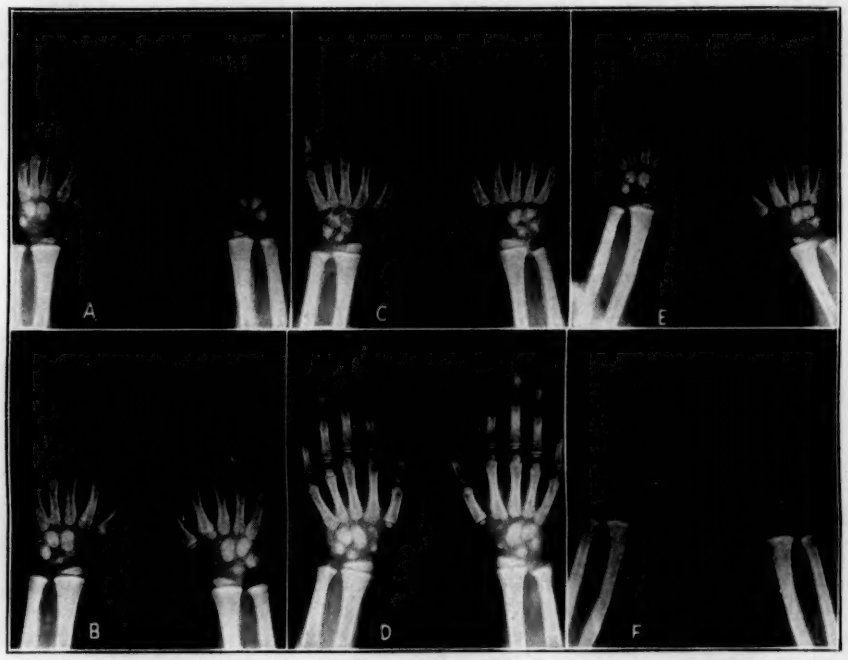

Fig. 1.—Roentgenograms, *A*, of J. E. at 59 months of age and *B*, at 68 months; *C*, of F. V. at 57 months and *D*, at 66 months, and *E*, of G. E. at 39 months and *F*, at 47 months.

56 to 81 mg. of phosphorus per kilogram. Cereal foods provided 13 per cent of the total calories, fruits (prunes, apple sauce, bananas and orange juice) 13 per cent, vegetables (green beans, carrots and potatoes) 7 per cent, butter 8.6 per cent and sugar 5.5 per cent. In the last four months two changes were made in the diet: (1) During periods 2 and 3 white bread and a refined wheat cereal were used in place of the commercial whole wheat bread (so called) and whole wheat breakfast cereal fed during period 1, and canned tomatoes were substituted for green beans, and (2) during the last two months (period 3) the protein ingestion was decreased from 3.4 Gm. to 2.6 Gm. per kilogram. During the first seven

months of the study (periods 1 and 2), it was believed that since the children had received adequate amounts of protein and were well stocked with nitrogen a study of nitrogen retentions with lower ingestions should determine the amount needed by well nourished children, for it seemed possible that the high requirements given in previous reports (Daniels and co-workers,[6] Hawks and co-workers [7]) might have been based on studies of undernourished children. These modifications, together with the increase in caloric needs as the children grew, brought about slight changes in the caloric distribution, so that cereals provided 13 per cent of the calories, fruit 16 per cent, vegetables (including potatoes) 8.5 per cent, butter 12.5 per cent and sugar 7.0 per cent. Again meat, eggs and milk were the chief sources of protein. Throughout the study each child received daily 3,000 U. S. P. units of vitamin D, in the form of 7.2 cc. of cod liver oil and 8 drops of viosterol in oil, given in two portions in orange juice between meals. The antirachitic effect of the vitamin was reenforced by exposing the children for ten minutes daily to the ultraviolet rays of a sun lamp. The ascorbic acid content of the diet during the first period, obtained by an analysis of all the foods, averaged 5.6 mg. per kilogram for the 2 older boys and 6.4 mg. for the younger. During periods 2 and 3 the intake of vitamin C from orange juice, canned tomatoes and bananas, calculated from theoretic values, averaged 6.7 mg. per kilogram for the 2 older boys and 7.7 mg for the younger.

With the exception of eggs, meat and cereal, the cooked food was prepared in quantity and stored in airtight containers in a refrigerator at a low temperature. Bread for each child came from a single loaf, which was sliced, weighed and wrapped in waxed paper at the beginning of the five day period. Similarly, the meat was chopped, freed from connective tissue, weighed and wrapped in serving portions and frozen. Sufficient egg and orange juice also were mixed at the beginning of the period and stored, an aliquot being taken for each serving. Since it was not possible in all cases to hold all foods for the two successive five day periods, a fresh supply was prepared and an aliquot analyzed for each of the five day periods.

The preparation of the food, feces and urine for analysis, as well as the methods used for determining the calcium, phosphorus and nitrogen content, were the same as those described in a previous report,[8] the only exception being that the calcium content of the urine was determined directly and subsequently checked by determinations on ashed samples.

OBSERVATIONS

Physical Development.—Data pertaining to the physical development of the children are given in table 1. At the beginning of the study J. E. was 5.2 per cent above the average in weight for height, according to

6. Daniels, A. L.; Hutton, M. K.; Knott, E. M.; Wright, O. E.; Everson, G. J., and Scoular, F.: A Study of the Protein Needs of Preschool Children, J. Nutrition **9**:91, 1935.

7. Hawks, J. E.; Bray, M. M., and Dye, M.: The Influence of Diet on the Nitrogen Balances of Pre-School Children, J. Nutrition **15**:125, 1938.

8. Daniels and others (footnotes 5 and 6).

TABLE 1.—*Data Pertaining to the Physical Development of Three Preschool Boys Fed Diets of High and Medium Protein Content*

Child	Period	Date	Age, Mo.	Initial Height, Cm.	Deviation of Initial Height from Average for Age,* per Cent	Final Height, Cm.	Deviation of Final Weight from Average for Age,* per Cent	Average Gain in Height per Day, Cm.	Deviation of Gain in Height from Average for Age,* per Cent	Initial Weight, Kg.	Deviation of Initial Weight from Average for Height,* per Cent	Final Weight, Kg.	Deviation of Final Weight from Average for Height,* per Cent	Average Gain in Weight per Day, Gm.	Deviation of Gain in Weight from Average Gain,* per Cent	Date of Roentgenogram	Chronologic Age	Skeletal Development † According to Harvard Standard § Todd Standard,‡	50th Percentile	90th Percentile
J. E.	1, 2	9/18-4/15	59-66	103.4	−5.4	108.7	−3.5	0.025	+44	17.9	+5.2	19.9	+7.9	9.5	+48	9/19	4 yr. 11 mo.	3 yr.	4 yr.	2 yr. 6 mo.
	3	4/15-6/26	66-68	108.7	−3.5	111.0	−3.1	0.032		19.9	+7.9	20.6	+7.3	10.1		6/ 6	5 yr. 7 mo.	<5 yr.	6 yr.	3 yr. >6 mo.
F. V.	1, 2	9/18-4/15	57-64	105.2	−2.4	111.0	0	0.028	+62	16.4	−7.1	19.8	+3.0	15.9	+167	9/19	4 yr. 9 mo.	4 yr. 3 mo.	5 yr. 6 mo.	3 yr.
	3	4/15-6/26	64-66	111.0	0	113.1	+0.3	0.029		19.8	+3.0	21.0	+6.0	18.3		6/ 6	5 yr. 6 mo.	6 yr.	6 yr. 6 mo.	4 yr. 6 mo.
G. E.	1, 2	9/18-4/15	39-46	93.0	−4.7	99.0	−2.4	0.028	+73	14.4	0	17.1	+6.3	12.6	+78	9/19	3 yr. 3 mo.	2 yr. 9 mo.	3 yr.	1 yr. 6 mo.
	3	4/15-6/26	46-48	99.0	−2.4	101.5	−1.0	0.035		17.1	+6.3	17.4	+3.7	5.1		6/ 6	3 yr. 11 mo.	<4 yr.	4 yr. 6 mo.	3 yr.

* Iowa Child Welfare Research Station.[9]

† Dorothy I. Stunz evaluated the roentgenograms.

‡ Todd and others.[3]

§ Vogt and Vickers.[4]

the standards given in "Physical Traits of Young Children," [9] prepared by the Iowa Child Welfare Research Station; G. E. conformed to the average, and F. V. was 7.1 per cent below the average. All 3 of the children were considerably below the average in height for age—J. E. 5.4 per cent, F. V. 2.4 per cent and G. E. 4.7 per cent. At the end of the study, in June, J. E. and G. E. were only 3.1 per cent and 1.0 per cent, respectively, below the average in height for age, while F. V. was 0.3 per cent above the average. Estimations based on weight for height showed that J. E. was 7.3 per cent, F. V. was 6 per cent and G. E. was 3.7 per cent above the average in weight. During the nine months of the study, J. E. gained 44 per cent more in height than the average for his age, F. V. 62 per cent more and G. E. 73 per cent more. In weight the boys gained 48 per cent, 167 per cent and 78 per cent, respectively, more than the average.

Comparison of the first roentgenograms taken two days after admission to the metabolism ward with the Todd standards of osseous development for age indicated that all 3 children were skeletally retarded; J. E. by one year eleven months and both F. V. and G. E. by six months. Comparisons with the Harvard ninetieth percentile standard, however, showed them to have considerably greater retardation: two years five months for J. E. and one year nine months for F. V. and G. E. In comparison with the fiftieth percentile Harvard standard, J. E. had a retardation of only eleven months and G. E. of three months, while F. V's. development was considerably in advance of his chronologic age. In June, at the end of the study, there were similar discrepancies, although the development of all 3 children had progressed and was much nearer to that considered normal for their respective chronologic ages by all standards. J. E. still had a retardation of more than seven months by the Todd standard; F. V.'s development was six months in advance of his age and that of G. E. conformed closely to the standard. In comparison with the Harvard fiftieth percentile standard, the skeletal development of all 3 children was ahead of their respective chronologic ages, while according to the nineteenth percentile Harvard standard they all still showed considerable retardation: somewhat more than one year seven months for J. E., one year for F. V. and eleven months for G. E.

Results of the Metabolic Investigation.—The investigation on metabolism, for which data are given in table 2, was divided into three periods: the first, from September 18 to February 18, comprised thirteen balance periods of five days, during which the children received whole grain

9. Physical Traits of Young Children, Iowa Child Welfare Research Station, State University of Iowa, Am. J. Dis. Child. **38**:541 (Sept.) 1929; Physical Traits of Iowa Infants, ibid. **42**:1137 (Nov.) 1931.

cereal foods and a diet high in protein; the second, from February 18 to April 15, consisted of four balance periods, during which refined cereal foods and a diet high in protein were used, and the third, from April 15 to June 26, was composed of seven balance periods, during which the children were fed refined cereals and a diet lower in protein. To save space, averages only are given here. Final averages, weighted, give the results of the entire study. The total ingestions and retentions for each ten day balance period are shown in figure 2.

Ingestions of calcium in proportion to body weight were somewhat lower at the end of the study than at the beginning, since the children had increased in weight and the amount of milk fed was kept constant.

TABLE 2.—*Data from Consecutive Mineral*

				Calcium								Phos	
				Ingestion per Kg. Mg.		Excretion in Feces, Mg.		Excretion in Urine, Mg.		Retention per Kg., Mg.		Ingestion per Kg., Mg.		Excretion in Feces, Mg.	
Child	Period	Average Weight, Kg.	Number † of 5 Day Balance Periods	Average	Range	Average	Range	Average	Range	Average	Range	Average	Range	Average	Range
J. E.	1	18.7	13	63	62-65	914	871-959	100	72-130	9.4	6.2-11.3	73	70-75	514	484-565
	2	19.4	3	60	59-63	848	828-889	77	63- 84	12.1	11.9-12.4	67	65-71	456	448-471
	3	20.4	7	56	54-57	816	769-856	79	67- 88	11.9	10.8-13.8	59	58-59	398	391-424
	Average*	19.4		61		875		91		10.9		68		471	
F. V.	1	18.2	13	65	60-70	936	890-974	75	66- 87	9.7	7.0-12.8	74	70-80	440	391-469
	2	19.7	4	59	57-61	935	883-974	80	73- 85	6.4	4.1- 9.3	65	63-66	452	408-489
	3	20.6	7	55	53-56	839	828-850	63	49- 81	11.4	10.3-12.2	57	56-58	347	334-368
	Average*	19.1		62		906		72		10.0		67		414	
G. E.	1	15.7	13	72	70-76	865	837-887	89	49-120	11.4	7.9-15.5	76	73-81	447	413-476
	2	16.8	4	66	66-66	887	876-911	57	47- 68	11.2	8.9-12.2	70	70-70	429	421-439
	3	17.4	7	64	61-65	830	754-883	78	70- 82	11.2	8.3-15.3	62	61-63	360	346-371
	Average*	16.4		69		857		81		11.3		71		418	

* Weighted.
† This figure does not include the six-day preliminary periods.

However, during all periods each child received more than 1.10 Gm. of calcium per day.

The calcium retentions of all 3 children showed considerable variation. High retentions in some cases can be explained by possible depletion, for example, at the beginning of the study, after the Christmas vacation of three weeks at home or after an illness (J. E., period 2). On the other hand, the low retention of F. V. during period 2 was possibly caused by an infection of the upper respiratory tract which occurred during the collection period and seemingly was too slight to interfere with the results of the test, since there was no apparent digestive disturbance. During this illness all foods were taken, although with some reluctance, and the slight elevations of temperature (99 to 101 F.) were present only one day. The consistently high retentions (higher in

2 cases than in period 1) at the end of the study, during May and June, are particularly noteworthy, since during the previous six months the children had ingested somewhat larger amounts of calcium in proportion to their weights and, so far as is known, adequate amounts of vitamin D. These high retentions, furthermore, were obtained when the skeletal development approached more closely the normal standards given by Todd. According to the ninetieth percentile Harvard standard, however, the development of all 3 children was still considerably retarded.

The theoretic ingestion of nitrogen during the first part of the study (periods 1 and 2) was kept constant at the level of 3.5 Gm. of protein per kilogram. On analysis, however, the amount actually ingested was

Balance Studies for Three Preschool Boys

phorus				Nitrogen									Retention Ratio
Excretion in Urine, Mg.		Retention per Kg., Mg.		Ingestion per Kg., Mg.		Excretion in Feces, Gm.		Excretion in Urine, Gm.		Retention per Kg., Mg.		Creatinine Height[a]	Nitrogen P — Ca (99%)
Average	Range	Average	Range	Average	Range	Average	Range	Average	Range	Average	Range		1.94
704	640-743	8.2	5.9-9.7	555	530-586	1.113	0.972-1.286	8.303	7.792-8.787	51	20-86	292	15:1
692	685-704	8.3	7.8-9.2	519	513-534	0.833	0.825-0.847	8.236	8.178-8.265	52	49-58	265	24:1
619	506-638	9.2	8.9-9.5	427	423-435	0.919	0.874-0.975	6.412	6.113-6.631	67	61-73	276	21:1
676		8.7		509		1.039		7.708		57		283	17:1
747	725-777	8.6	7.0-10.1	548	498-592	0.890	0.687-1.010	8.042	7.726-8.254	57	43-64	235	15:1
733	723-741	4.7	3.5-6.3	500	489-507	0.689	0.647-0.716	8.505	8.275-8.723	32	24-43	226	21:1
652	619-672	8.6	7.5-9.4	414	412-419	0.685	0.664-0.711	6.617	6.433-6.721	60	58-62	225	21:1
716		8.2		500		0.797		7.681		56		232	18:1
631	592-657	7.8	6.0-9.9	549	513-594	0.951	0.812-1.103	6.972	6.728-7.243	44	37-51	285	21:1
622	598-644	7.8	7.6-8.1	507	505-510	0.786	0.774-0.800	7.108	6.803-7.382	42	27-58	284	19:1
579	567-591	8.1	6.5-10.0	425	423-433	0.789	0.733-0.850	5.716	5.562-5.877	52	42-63	280	22:1
614		7.9		505		0.876		6.616		46		283	21:1

found to be slightly lower, that is, 3.41 Gm. per kilogram. During the several metabolism periods this figure varied slightly because of variations in the composition of the different purchases of food. As the children increased in weight, the amount ingested per kilogram decreased slightly but never fell below 3 Gm. per kilogram except during period 3, when the amount of protein fed was lowered to 2.6 Gm. per kilogram. In relation to the weight of the children, retentions with these lower ingestion levels were 5.3, 18.2 and 31.4 per cent higher during period 3 than during period 1.

The amount of phosphorus ingested was high throughout the study, averaging 7.4 mg. per kilogram during period 1 and 5.9 mg. during period 3, and was from 0 to 17 per cent higher than the amount of calcium ingested. In line with the higher retentions of calcium and nitrogen during period 3, the phosphorus retentions also were slightly

higher in 2 cases and the same in the third, even though the ingestions were lower in all cases, which suggests that the lower amount given was sufficient.

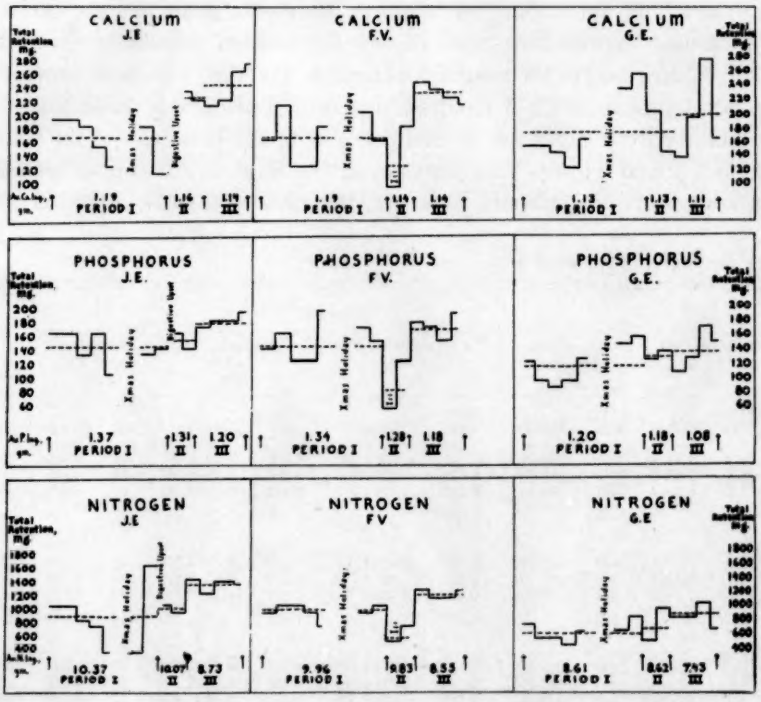

Fig. 2.—Total retentions of calcium, phosphorus and nitrogen by the 3 boys during each ten day balance period. The dotted lines indicate the average retention at given ingestion levels. The low retentions by F. V. in period 2 occurred during a slight illness.

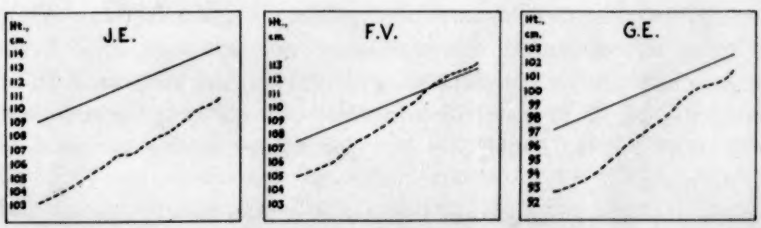

Fig. 3.—Comparisons of the gains in height of the preschool boys (dotted lines) with their theoretically normal gains (solid lines) as given by the Iowa Child Welfare Research Station. J. E. gained 44 per cent, F. V. 62 per cent and G. E. 73 per cent more than the average.

COMMENT

The persistently high retentions of calcium, the lower than average heights at the beginning of the study and the rapid approach to average height (fig. 3), the roentgenographic indications of retarded skeletal development and the low retention ratios $\left(\frac{\text{nitrogen}}{\text{phosphorus} - \text{calcium}\ \frac{[99\ \text{per cent}]}{1.94}}\right)$ which average 19:1 throughout the study, all point to the conclusion that the 3 children were definitely undernourished in spite of the fact that their weights for height were within the normal range and they gave the impression of being physically fit.

As was previously stated, it was anticipated that high calcium retentions would obtain during the first months of the study, that these would gradually decrease and that the final figures would be indicative of the amount of calcium normal well nourished children should retain. Therefore, it was a surprise to find that the average retentions in relation to weight during period 3 (table 2) were as high as in period 1 in 1 case (G. E.) and higher in the other 2 cases (J. E. and F. V.), even though the roentgenograms at the end of the study indicated normal skeletal development (Todd scale) for 2 of the children (F. V. and G. E.) and for the third a retardation of only seven months. Furthermore, during period 3 there was a more rapid gain in height (the average being 0.032 cm. per day for J. E., 0.029 for F. V. and 0.035 for G. E.) than in periods 1 and 2, in which the gains averaged 0.025, 0.028 and 0.028 cm., respectively. The reason for this more rapid growth in period 3 is not clear. Was too little calcium supplied to allow for saturation of the tissues and growth, or did the summer sunshine contribute something not yet appreciated? During periods 1 and 2 (September to April), the children were out of doors an average of thirty-seven minutes per day, whereas during period 3 the playtime out of doors averaged one hundred and forty-six minutes. The calcium intake in all periods (53 to 76 mg. per kilogram) as judged by the needs of children of this age was high. Outhouse and associates found that for children whose tissues were seemingly well saturated with calcium 32 to 44 mg. per kilogram was sufficient, whereas in a previous report Daniels and co-workers stated that preschool children needed 45 to 50 mg. per kilogram. Furthermore, retentions were equally high in 2 cases and higher in a third during period 3, when ingestions were lower. All factors which control the speed with which depleted tissue becomes replenished are not known. In the present study, according to accepted standards, the children received sufficient vitamin D. Were the calcium ingestions during period 1 too low to allow for saturation and optimum growth, or must there be a certain degree of saturation before optimum growth is possible?

During the two hundred and eighty-two days of the study, the 3 children gained 2.69, 4.63 and 3.01 Kg., considerably more in all cases than the average given by the Iowa Child Welfare Research Station for children of similar ages. The theoretic amounts of calcium retained, estimated to be 1.28 per cent of the gains in weight (Mitchell [10]), were 34, 59 and 38 Gm., figures lower in 2 cases than the values (60, 54 and 52 Gm.) obtained by multiplying the total number of calendar days of the study (282) by the average retentions per day of the several balance periods, on the assumption that these average values are representative. These high calcium values suggest that the calcium content of the added tissue was larger than the theoretic calcium content of the tissue gained by average children of the same ages, that is 23, 22 and 22 Gm. The higher calcium content of the new tissue is also indicated by the percentage calcium contents of the added tissue, 2.16, 1.14 and 1.75, which were obtained by dividing the daily retention of calcium multiplied by 100 by the daily gain in weight. The lowest percentage obtained was for the child (F. V.) with the least skeletal retardation and the highest for the child (J. E.) with the most retardation. Mitchell's figure of 1.28 per cent is higher than that for our child with the least retardation, which suggests that his figure also may have been based on data obtained for children with skeletal retardation. Sherman and Hawley [11] gave as the average calcium retention for children between 3 and 11 years of age the value of 11 mg. per kilogram per day, a figure which compares with the average retentions of the skeletally retarded children of the present study.

The calcium-phosphorus retention ratios were 1.25, 1.22 and 1.43. The child who was the least skeletally retarded but the most underweight for his age (F. V.) had the lowest ratio, 1.22, while the child who gained the most in height (G. E.) had the highest retention ratio, 1.43. F. V. apparently was building soft tissue at a faster rate than bone, while G. E. was building more bone.

A comparison of the final calcium retentions of the children under observation with those reported by Outhouse and associates and with the average of the group reported on previously by Daniels and co-workers suggests that the tissues were not yet saturated. By the Todd standard, the skeletal development of all the children at this time was normal, or not far below that for their respective chronologic ages. By the standards of the Harvard ninetieth percentile, however, the skeletal ages of the children were from one year to two years below their chronologic

10. Mitchell, H. H.: The Dietary Requirement of Calcium and Its Significance, in Actualités scientifiques et industrielles, Paris, Hermann & Cie, 1939, no. 18, p. 771.

11. Sherman, H. C., and Hawley, E.: Calcium and Phosphorus Metabolism in Childhood, J. Biol. Chem. **53**:375, 1922.

ages. Do the Todd standards represent the average child and those of the Harvard ninetieth percentile the optimum so far as bone development is concerned? Assuming that both the Todd and the Harvard standards are based on representative samplings, then 80 per cent of the children of the nation are undernourished with regard to calcium, a figure which corresponds with the high incidence of dental caries among children. Whereas from 32 to 44 mg. per kilogram of calcium (Outhouse and associates) may well be sufficient to meet the needs of children of the age considered whose tissues are well saturated with calcium, of whom there appear to be not more than 20 per cent (according to the Harvard studies), the majority of children, it is believed, should receive more, at least until their osseous tissues have become replenished. However, in the absence of calcium retentions for children whose osseous development corresponds to the standards of the Harvard ninetieth percentile, final conclusions regarding optimum amounts must be withheld.

The amount of phosphorus needed by children receiving sufficient vitamin D is determined by the rate of growth and by the state of nutrition as regards both calcium and nitrogen. In the present study, assuming that the amount of calcium fed was adequate, the amount of phosphorus also seems to have been sufficient, since the average ratio of calcium to phosphorus was 1.08. Furthermore, the high percentages of phosphorus excreted in the urine (51, 56 and 53 per cent of the intake) and the fact that equally high retentions were obtained in 2 cases and slightly higher retentions in a third with lower ingestions during period 3 seem to indicate that enough had been given during all periods. During period 1 retentions averaged 8.2, 8.6 and 7.8 mg. per kilogram and during period 3, 9.2, 8.6 and 8.1 mg. Average retentions for the entire period of study, 8.7, 8.2 and 7.9 mg. per kilogram, are in line with those reported previously (Daniels and associates [5]), which were between 6 and 9 mg. per kilogram. Since the children in the present study are known to be skeletally retarded and 1 at least (F. V.) has a low muscular development, as was shown by the low creatinine-height [3] coefficient (Daniels and associates [12]), the retentions of phosphorus were undoubtedly higher than obtained for the well nourished child. It seems, therefore, that the low values, of 5 to 6 mg. per kilogram, which were reported in the former study were based on balance studies of more nearly physically fit children.

Nitrogen retentions of the 3 boys under consideration seem to indicate that previously their protein needs had been fairly well met. Creatinine-

12. Daniels, A. L.; Hutton, M. K., and Neil, B.: Relation of the Creatinine-Height Coefficient to Various Indexes of Nutrition, Am. J. Dis. Child. **55**:532 (March) 1938.

height [8] coefficients averaged at the beginning 292 and 235 for the 2 older boys and 285 for the younger and at the end of the study 276, 225 and 280, respectively. With what is believed to be an adequate ingestion of protein, 3.41 Gm. per kilogram, nitrogen retentions averaged 51, 57 and 44 mg., respectively (period 1, table 2). During period 3, when ingestions were lowered to 2.6 Gm. of protein per kilogram, retentions were higher in all cases, averaging 67, 60 and 52 mg. per kilogram, respectively. Coexistent with these higher retentions were greater daily gains in weight by 2 boys (J. E., 10.1 Gm., and F. V., 18.3 Gm. [table 1]). While the third, G. E., gained less than during period 1, his gain in weight still exceeded the average for children of his age. All 3 boys also made greater gains in height during this period than in periods 1 and 2 and considerably greater gains than the average for their ages. That these higher nitrogen retentions are not related to the greater availability of the nitrogen of the diet containing the more refined cereals is shown by the percentage of nitrogen excreted in the feces and the coefficients of utilization, which averaged 89.7 per cent with the less refined cereal foods (period 1) and 90 per cent with the more refined cereals (period 3), differences within the limits of experimental error.

Since these higher nitrogen retentions during period 3, when the ingestion levels were lower (2.6 Gm. of protein per kilogram), were coexistent with more rapid gains in height and in weight, it is possible that the belief expressed by Hawks and associates [7] that large amounts of protein (4 Gm. per kilogram) should be fed was based on the result of studies of skeletally retarded children who previously had been adequately fed as regards protein. In the absence of data on their metabolism of calcium and phosphorus, however, we can present only a tentative hypothesis. The children studied by these authors received from 380 to 1,700 U. S. P. units of vitamin D,[13] whereas the children of the present study were given 3,000 U. S. P. units and in addition daily ten minute exposures to an ultraviolet ray lamp. Possibly the lesser amount of vitamin D used in the former study was insufficient to bring about rapid absorption and deposition of calcium and phosphorus, more particularly in the period of lower protein ingestion which came first in each series. It is well known that infants with rickets require larger amounts of vitamin D than normal infants. The same may hold for older children with retarded skeletal development. It will be noted that during the period of low protein ingestion in the study by Hawks and associates

13. One pearl of "haliver oil 250 d," distributed by Parke, Davis & Co., which was used by Hawks and associates in experiment II, contained, according to published literature, not less than 1,700 U. S. P. units of vitamin D per gram, whereas the cod liver oil used in their experiment I, according to a statement of the company marketing it, contained not less than 380 U. S. P. units per gram.

there was little gain in weight. In the period of high protein ingestion the gain in weight was higher but considerably less than that with the diets lower in protein used in the present study. Adult tissues well nourished as regards nitrogen will retain only the amount needed to meet the normal catabolic processes. In young tissues there is not only a need to replace the nitrogen lost through the normal catabolic processes; there is a direct relation as well between growth and retention. Therefore, the efficiency of any given protein is judged by the rate of growth and the proportion retained with the lowest ingestion levels when all other essential constituents are present in optimum amounts.

The gains in height of the children given the diets containing 3 and 4 Gm. of protein per kilogram (Hawks and associates [7]) were much lower than those of the children of the present study who received only 2.6 Gm. Gains in weight also were conspicuously lower than those of 2 children of the present study who received the diet lower in protein. The high retentions with the low levels of protein ingestion and the more rapid gains in height and weight of the children in the present study occurred in the late spring and early summer when they were out of doors two and a half hours (an average of one hundred and forty-five minutes) per day. If these higher retentions are the result of more ultraviolet ray irradiation, the assumption regarding the cause of the low retentions in the study of Hawks and associates would seem tenable.

The data of the present study suggest that from 2.6 to 3 Gm. of protein per kilogram (nitrogen $\times$ 6.25) will supply enough protein for the average child, provided a sufficient amount of animal protein and enough vitamin D are included. The validity of this figure is emphasized by the fact that high retentions were obtained for children who were still somewhat below their optimum development as shown by their roentgenograms and who were gaining in height and weight considerably faster than the average child. It has been suggested that the requirement for calcium of well stocked children may be somewhat less than the requirement for the "average child;" the potentially large child may need slightly more. The same principle holds for the nitrogen requirement; the well stocked child will need less than the "average child." These figures (2.6 to 3 Gm. of protein per kilogram) are slightly lower than the figure obtained in a previous study,[6] in which it was concluded that 1.5 Gm. per pound (454 Gm.) is needed by the average child of the age considered.

SUMMARY

The physical development of 3 skeletally retarded boys of preschool age has been studied during a nine month period and comparisons made of the calcium, phosphorus and nitrogen retentions, gains in height and

weight and changes in the bone development from one balance period to the other as shown by roentgenograms of the hands and wrist bones. So far as possible, calcium and phosphorus ingestions were kept constant throughout the study, through the inclusion of a constant amount of milk in the diet. As the children increased in weight, the values for calcium and phosphorus per kilogram decreased slightly. Two levels of nitrogen ingestion were used, 3.4 Gm. and 2.6 Gm. of protein per kilogram. Skeletal ages were determined by four standards: those of Flory, Todd and the fiftieth and the ninetieth Harvard percentile.

During the period of study, the children gained 44, 62.5 and 73 per cent more in height and 48, 167 and 78 per cent more in weight than the average for their ages. The average calcium, phosphorus and nitrogen retentions remained high throughout the study, the retentions at the end periods being in some cases as high as and in others higher than in the early periods. Decrease in the nitrogen ingestion did not influence the nitrogen retentions, since high retentions were obtained with the lower ingestions. These higher retentions were coexistent with greater gains in height in 2 cases and in weight in 2 cases and occurred during April, May and June, when more time was spent out of doors. The significance of this is discussed in relation to low retentions with higher ingestions observed during a previous study.

The skeletal ages of the children, which were from six months to one year eleven months below the chronologic ages (Todd standard), tended to approach the normal by all standards. In comparison with the Todd standard at the end of the study, the development of 1 child was normal, of 1 was advanced and of 1 was slightly below the chronologic age. The development of all 3 was somewhat in advance of the chronologic ages according to the Harvard fiftieth percentile standards but still considerably retarded according to the ninetieth percentile standards. In view of the high retentions of calcium and phosphorus during the later balance periods of the study, it is concluded that the Todd standards of skeletal development represent the development of the average child and the Harvard ninetieth percentile standards that of the optimally nourished child as regards calcium. On the bases of the representative samplings, it appears that not more than 20 per cent of the children of the age considered are well nourished.

A comparison of the nitrogen retentions at the two levels of protein ingestion in relation to the gains in height and in weight leads to the conclusion that 2.6 Gm. of protein per kilogram is sufficient for the average child of the preschool age. The potentially large child may need more.

LUMBAR PUNCTURE AS A FACTOR IN THE PATHOGENESIS OF MENINGITIS

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Meningitis is presumed to arise in one of three general ways: Organisms may reach the subarachnoid space by direct traumatic implantation; infection may extend to the meninges from an adjacent lesion, as in some cases of virulent mastoiditis with progression of the infection through the temporal bones, or organisms gaining access to the general circulation from a focus of infection at any site, however remote, may succeed in reaching the meninges by passing the blood-brain barrier.

Lumbar puncture, performed for diagnosis, entails the risk of producing meningitis. The danger involved in a break in aseptic technic is clearly visualized and constantly borne in mind. Other dangers, related to the effect of lumbar puncture on the permeability of the blood-brain barrier and to the possibility of introducing bacteria-containing blood into the subarachnoid space, are less clearly understood and at times seem to be ignored. The uncertainty which surrounds the latter factors justifies an inquiry into their scope.

In an attempt to evaluate the role of lumbar puncture in the pathogenesis of meningitis, a survey has been made of cases of pneumococcic meningitis in infants and children. Pneumococcic meningitis was chosen for the survey because it is one of the common types of meningitis [1] and because the pneumococcus, unlike the meningococcus, shows no inherent predilection for attacking the meninges. The latter circumstance permits one to come closer to an evaluation of the part played by lumbar puncture as such. The frequency with which meningismus accompanies pneumonia makes it particularly important to ascertain whether one is justified in resorting to diagnostic lumbar puncture without fear, or whether under certain circumstances the wisdom of this procedure can be questioned. With the new chemotherapeutic agents

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1. (*a*) Fothergill, L. D., and Sweet, L. K.: Meningitis in Infants and Children with Special Reference to Age-Incidence and Bacteriologic Diagnosis, J. Pediat. **2**:696, 1933. (*b*) Fothergill, L. D.: Hemophilus Influenzae (Pfeiffer Bacillus) Meningitis and Its Specific Treatment, New England J. Med. **216**:587, 1937.

now available, the prognosis may be affected by the ability to make an early diagnosis.[2]

MATERIAL

The general survey includes the cases of 36 patients with pneumococcic meningitis treated in the Babies Hospital from 1930 to 1939, inclusive, and of 171 patients treated in the Harriet Lane Home, of the Johns Hopkins Hospital, from 1912 to 1938, inclusive. An attempt has been made, by searching the clinical and pathologic files, to include the cases of all patients with pneumococcic meningitis admitted during those intervals. The general survey also includes the cases of patients with pneumococcemia treated during the past six to eleven years in the children's services of the New Haven Hospital, the New York

TABLE 1.—*Factors Predisposing to the Development of Meningitis*

Predisposing Factor	Babies Hospital 36 Cases (1930-1939)		Harriet Lane Home 171 Cases (1912-1938)		Both Series, 207 Cases, Chief Predisposing Factor	
	Participating Factor	Chief Factor	Participating Factor	Chief Factor	Number	Per Cent
Pneumonia before onset	11	8	55	55	63	30
Pneumonia during meningitis	5	1	32	24	25	12
					Total	42
Otitis media, mastoiditis and sinusitis	27	18	94	58	76	37
Infection of the upper respiratory tract	3	2	22	8	10	5
Operations on the head, the nose and the throat	4	0	2	2	2	1
Injury to the head	3	2	1	1	3	1
					Total	44
General lowered resistance	1	1	5	5	6	3
Trauma and operations on structures other than the head	2	2	2	2	4	2
No primary infection evident	2	2	10	10	12	6
Other conditions	1	0	10	6	6	3

Hospital, the Boston Children's Hospital, the Harriet Lane Home and the Babies Hospital.

Pneumococcic meningitis is rarely encountered except in cases in which a pneumococcic infection has already been established in some part of the body. In table 1 are summarized the data regarding the

2. (*a*) Finland, M.; Brown, J. W., and Raugh, A. E.: Treatment of Pneumococcus Meningitis, New England J. Med. **218**:1033, 1938. (*b*) Hodes, H. L.; Gimbel, H. S., and Burnett, G. W.: Treatment of Pneumococcic Meningitis with Sulfapyridine, J. A. M. A. **113**:1614 (Oct. 28) 1939. (*c*) Rhoads, P. S.; Hoyne, A. L.; Levin, B.; Horswell, R. G.; Reals, W. H., and Fox, W. W.: Treatment of Pneumococcus Meningitis, ibid. **115**:917 (Sept. 14) 1940. (*d*) Neal, J. B.; Applebaum, E., and Jackson, H. W.: Sulfapyridine and Its Sodium Salt in the Treatment of Meningitis Due to the Pneumococcus and Haemophilus Influenzae, ibid. **115**:2055 (Dec. 14) 1940.

frequency and the location of lesions due to infections or trauma which may have contributed to the production of meningitis. In only a few of the cases was such a focus absent, and in many there was more than one focus. The columns labeled "Participating Factor" in table 1 show the total number of cases in which each lesion or factor was present, while in those with the heading "Chief Factor" the single most important factor in each case is indicated. Both in the cases from the Harriet Lane Home and in those from the Babies Hospital the factor of infection or trauma about the head is numerically in first place, with pneumonia next in frequency. The data of Neal, Jackson and Appelbaum [3] showed a similar distribution.

A blood culture positive for pneumococci was obtained in 53 per cent of the cases of pneumococcic meningitis studied. In all probability bacteremia was present in a much higher percentage, because in many of the earlier cases blood culture was not performed and in many others the results of only one or two cultures were recorded.

It is to be noted that in 13 cases, or 6 per cent, lumbar puncture was performed before the onset of meningitis. The chronologic relation of lumbar puncture to the subsequent meningeal infection is indicated in table 2, which gives data for the 13 cases.

The age of the patients in the 207 cases of pneumococcic meningitis is given in table 3; it is significant that approximately 80 per cent of the patients with meningitis were under 2 years of age, the age period when resistance to infection is lowest. Others [1a] have found a similar age incidence for meningitis. A lack of immunity of the blood to pneumococci has been shown to exist between the ages of 10 days and 2 years.[4] There is an analogous absence of bactericidal power against Haemophilus influenzae during a slightly later age period, between the ages of 2 months and 3 years.[5]

The types of pneumococci recovered in the 207 cases of pneumococcic meningitis are given in table 4. The scattered distribution supports

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3. (*a*) Neal, J. B.; Jackson, H. W., and Appelbaum, E.: Comprehensive Study of Meningitis Secondary to Otitic or Sinus Infection, Ann. Otol., Rhin. & Laryng. **43**:658, 1934. (*b*) Neal, Appelbaum and Jackson.[2d]

4. Sutliff, W. D., and Finland, M.: Antipneumococcic Immunity Reactions in Individuals of Different Ages, J. Exper. Med. **55**:837, 1932. Finland, M., and Sutliff, W. D.: Immunity of Human Subjects to Strains of Pneumococci Other Than Types I, II and III, ibid. **57**:95, 1933.

5. Fothergill, L. D., and Wright, J.: Influenzal Meningitis: The Relation of Age Incidence to the Bactericidal Power of Blood Against the Causal Organism, J. Immunol. **24**:273, 1933.

TABLE 2.—*Data for Cases of Pneumococcic Meningitis in Which Lumbar Puncture Preceded the Onset of Meningitis*

Name, Age, Year	Predisposing Factors	Type of Pneumococci in Cultures: Blood	Type of Pneumococci in Cultures: Spinal Fluid	Result	Data on Spinal Fluid
			Harriet Lane Home		
J. E. 17 mo. 1913	Pneumonia; pulmonary abscess; empyema; peritonitis	.....	Not typed	Died	1st day: fluid clear, 20 cells; no record of organisms being present 5th day: 100 cells; many pneumococci
W. S. 11 mo. 1917	Repair of cleft palate and lip; otitis media	.....	Not typed	Died	8th day after repair: clear fluid, 4 cells 17th day: cloudy fluid Autopsy: pneumococci
A. D. 7 yr. 1925	Fracture of the skull; abscess of the brain (?)	Group 4	Group 4	Died	1½ months before admission: normal 2 days before admission: normal 1st day in hospital: cloudy fluid containing pneumococci
W. R. 20 mo. 1925	Pneumonia; otitis media	.....	Not typed	Died	1st day: clear fluid 2d day: no fluid obtained 3d day (cisternal puncture): fluid clear, 7 cells 4th day (autopsy): exudate containing pneumococci over brain
H. B. 11 mo. 1926	Otitis media; meningococcic meningitis and hydrocephalus	Group 4	Group 4	Died	Several previous lumbar punctures and injections of serum for meningococcic meningitis: 1st day of present illness: 80 cells, no organisms 10th day: 23 cells, no organisms 14th day: 16 cells, no organisms 25th day (ventricular puncture): fluid clear, pressure increased 28th day: 64 cells, many pneumococci
D. P. 2 mo. 1927	Otitis media; infection of the upper respiratory tract; tetany (?)	.....	Not typed	Died	1st day: no fluid obtained 2d day (cisternal puncture): fluid clear 14th day (autopsy): pneumococcic meningitis
E. T. 3 mo. 1928	Osteomyelitis; dehydration	.....	Group 4; staphylococcus (?)	Died	2d day: clear fluid 3d day (autopsy): pneumococcic meningitis
H. H. 4 mo. 1933	Pneumonia; otitis media	Type 12	Type 12	Died	11th day: clear fluid, no cells, normal pressure 16th day: cloudy fluid, 230 cells, many pneumococci
M. J. 2 mo. 1938	Pneumonia; otitis media; congenital syphilis; tetany (?)	Type 12	Type 12	Died	3d day: clear fluid 7th day: clear fluid 14th day: cloudy fluid, many pneumococci
			Babies Hospital		
R. S. 5½ mo. 1934	Otitis media; infection of the respiratory tract	Type 4	Type 4	Died	1st day: fluid normal except for fresh red blood cells and 29 white blood cells 1st day (2 hours later): fluid cloudy, many pneumococci
J. M. 1 mo. 1937	Pneumonia; cellulitis; subcutaneous abscesses; otitis media; endocarditis and osteomyelitis at autopsy	Type 5; staphylococcus	Type 5; staphylococcus	Died	4th day: spinal fluid bloody, clear supernatant fluid; smear and culture negative for organisms 11th day (autopsy): meningitis

TABLE 2.—*Data for Cases of Pneumococcic Meningitis in Which Lumbar Puncture Preceded the Onset of Meningitis—Continued*

Name, Age, Year	Predisposing Factors	Type of Pneumococci in Cultures: Blood	Type of Pneumococci in Cultures: Spinal Fluid	Result	Data on Spinal Fluid
M. L. 10 mo. 1939	Pneumonia; otitis media; bilateral subdural hematoma; congenital syphilis; hydrocephalus	Type 14	Type 14	Died	5th day: traumatic puncture, no fluid obtained 8th day: spinal fluid slightly bloody, supernatant fluid xanthochromic Kline reaction 4+ 21st day (bilateral subdural taps): bloody fluid 33d day: lumbar puncture and injection of air; fluid normal 46th day: cloudy fluid, pneumococci on smear and culture
R. F. 6 yr. 1939	Otitis media; infection of the upper respiratory tract	Type 18	Type 18	Recovered after treatment with sulfanilamide and rabbit antiserum	1st day: fluid reported clear in another hospital 1st day (afternoon): fluid cloudy, contained pneumococci

the contention that no single type of pneumococcus can be regarded as meningotropic. A comparable diversity has been observed by others.[6]

Data concerning the relation between pneumonia and pneumococcic meningitis are incorporated in table 5. An attempt has been made to estimate the frequency with which pneumococcic meningitis complicates pneumonia. Pneumococcic meningitis occurred as a complication in 103 of 11,742 cases of proved or presumed pneumococcic pneumonia, that is, cases of pneumonia in which the pneumococcus was isolated or in which bacteriologic data were not given. This incidence may be compared with the figures given by Howard,[7] who stated that pneumococcic meningitis occurs as a complication in 1 to 2 per cent of cases of pneumonia in children.

The results of an investigation of the frequency of meningismus in cases of pneumonia are given in table 6. For this purpose the clinical records for all patients with pneumonia treated in the Babies Hospital

6. Finland, M.: The Significance of Specific Pneumococcus Types in Disease, Including Types IV to XXXII (Cooper), Ann. Int. Med. **10**:1531, 1937. Appelbaum, E.: Sulfanilamide and Related Compounds in the Treatment of Meningitis Secondary to Ear and Sinus Infections, Laryngoscope **48**:482, 1938. Shaffer, M. F.; Enders, J. F., and Wilson, J.: The Effect of Artificial Fever and Specific Antiserum on the Organisms Present in Cases of Type III Pneumococcus Meningitis, J. Clin. Investigation **17**:133, 1938. Ordman, D.: Pneumococcus Types in South Africa: A Study of Their Occurrence and Distribution in the Population and the Effect Thereon of Prophylactic Inoculation, Publ. South African Inst. M. Research **9**:1, 1938. Footnote 2. Neal, Jackson and Appelbaum.[8a]

7. Howard, C. P.: Pneumonia, in Christian, H. A.: Oxford Monographs of Diagnosis and Treatment, New York, Oxford University Press, 1931, vol. 10.

over a two year period have been examined. From the same material was ascertained the frequency with which lumbar puncture was performed in cases of pneumonia because of meningismus or other evidence of meningitis. It happens that bacteremia was not present in any of the cases in which the patient was subjected to lumbar puncture, and in none did meningitis occur.

TABLE 3.—*Age of Patients in Two Hundred and Seven Cases of Pneumococcic Meningitis*

Age, Years	Babies Hospital (1930-1939)		Harriet Lane Home (1912-1938)		Both Series	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
0 - 1.....	25	69	110	64	135	65.2
1 - 2.....	4	11	28	17	32	15.5
Over 2.....	7	20	33	19	40	19.3

TABLE 4.—*Type of Pneumococcus Recovered in Two Hundred and Seven Cases of Pneumococcic Meningitis*

Type of Pneumococcus*	Harriet Lane Home, 1912-1938, Number of Cases	Babies Hospital, 1930-1939, Number of Cases	Type of Pneumococcus	Harriet Lane Home, 1912-1938, Number of Cases	Babies Hospital, 1930-1939, Number of Cases
1	15	2	17	0	1
2	15	0	18	3	3
3	9	2	19	3	3
4	3	2	21	0	1
5	4	2	22	1	0
6	7	5	23	2	0
7	1	2	24	0	2
8	3	0	25	0	1
9	2	1	28	1	0
11	2	0	29	2	0
12	3	1	32	1	0
14	8	3	Group 4	42	1
16	1	0	Not typed	45	4

* More than one type of pneumococcus was isolated in 2 cases from the Harriet Lane Home.

Table 7 contains data from an analysis of 416 cases of pneumococcemia; it gives the incidence of meningitis in the cases in which lumbar puncture was performed and in those in which it was not. The cases were divided into two groups, on the basis of the patient's being over or under 2 years of age, because of the apparently greater susceptibility to meningitis of patients in the younger age group. The data show no significant difference between the percentage incidence of meningitis in the cases in which lumbar puncture was carried out and that in the cases in which it was not performed. Meningitis developed in approxi-

mately 30 per cent of the patients under 2 years of age and in approximately 10 per cent of those over 2 years of age, whether or not lumbar puncture was done. The number of patients subjected to lumbar punc-

TABLE 5.—*Incidence of Pneumococcic Meningitis as a Complication in Cases of Pneumonia*

	Pneumonia, Number of Cases	Pneumococcic Meningitis	
		Number of Cases	Per Cent
Harriet Lane Home (1912-1938).....	9,552	87	0.9
Babies Hospital (1930-1939).....	2,190	16	0.7

TABLE 6.—*Incidence of Meningismus in Three Hundred and Twenty-One Cases* of Pneumonia*

Pneumonia, Number of Cases	Meningismus		Lumbar Puncture			
	Number of Cases	Per Cent	Number of Cases	Per Cent	Bacteremia Present	Meningitis Followed
321	33	10	19	6	0	0

* From the Babies Hospital, 1935 and 1936.

TABLE 7.—*Incidence of Meningitis Among Patients with Pneumococcemia Who Did and Among Those Who Did Not Undergo Lumbar Puncture*

	Patients Under 2 Years of Age				Patients Over 2 Years of Age			
	Meningitis		No Meningitis		Meningitis		No Meningitis	
	Lumbar Puncture	No Lumbar Puncture	Lumbar Puncture	No Lumbar Puncture	Lumbar Puncture	No Lumbar Puncture	Lumbar Puncture	No Lumbar Puncture
New Haven Hospital.....	1	15	0	46	0	5	1	39
Boston Children's Hospital..	1	17	3	27	0	3	3	36
New York Hospital.....	0	5	3	14	1	2	1	12
Harriet Lane Home.....	3	22	5	48	0	1	1	28
Babies Hospital	2	11	3	28	0	5	2	22
	7 (33%)	70 (30%)	14 (67%)	163 (70%)	1 (11%)	16 (10%)	8 (89%)	137 (90%)

ture is small for statistical comparison, but the close agreement in the percentages is striking.

Interest in the possible danger of performing lumbar puncture in cases in which meningitis is suspected was stimulated by experimental evidence that in the presence of bacteremia this procedure can produce meningitis and by scattered reports in the literature of cases in which meningitis followed lumbar puncture.

REVIEW OF STUDIES ON THE EXPERIMENTAL PRODUCTION OF MENINGITIS

Experimental production of meningitis in animals has yielded such convincing evidence of the danger of lumbar puncture that a review of some of the work will be of help in evaluating those of the cases considered in this paper in which lumbar puncture had been done before the onset of meningitis.

Netter,[8] in 1887, found that infection may spread to the meninges by way of the blood stream. He produced meningitis in a rabbit by injecting into the lung material containing pneumococci, having first cauterized the brain through a trephine opening. The experiments of Austrian[9] on rabbits led to the conclusion that meningitis may develop in the presence of bacteremia when the meninges are not in a normal state. Having been unable to produce meningococcic meningitis by the intravenous injection of a standard suspension of organisms, he found that the same procedure resulted in meningitis if he injected intrathecally 1 to 2 cc. of normal rabbit serum thirty to fifty minutes before the intravenous injection. Of the 20 rabbits so treated, 3 died of typical meningitis. Two rabbits were killed an hour after injection, and smears showed meningococci in the meninges; the spinal fluid culture of 1 was positive for the organisms, that of the other was not. Seven of the rabbits recovered from symptoms related to the procedure in from thirty minutes to two hours. Eight died within eight to twelve hours, without meningitis. Austrian expressed the opinion that injection of serum into the subarachnoid space rendered the meninges more susceptible to infection through irritation and hyperemia. However, he mentioned that the introduction of a needle into the subarachnoid space of a rabbit is difficult and causes injury to the cord. Amoss and Eberson[10] were unable to duplicate Austrian's results unless the cord was traumatized, and they expressed the belief that such trauma was the chief factor in producing the meningitis.

By carefully controlled experiments, chiefly with cats, Weed, Wegeforth, Ayer and Felton[11] obtained conclusive evidence that the with-

8. Netter, A.: De la méningite due au pneumocoque (avec ou sans pneumonie), Arch. gén. de méd. **19**:257, 434, 1887.

9. Austrian, C. R.: Experimental Meningococcus Meningitis, Bull. Johns Hopkins Hosp. **29**:183, 1918.

10. Amoss, H. L., and Eberson, F.: Mode of Infection in Epidemic Meningitis, J. Exper. Med. **29**:605, 1919.

11. (*a*) Weed, L. H.; Wegeforth, P.; Ayer, J. B., and Felton, L. D.: The Production of Meningitis by Release of Cerebrospinal Fluid, J. A. M. A. **72**:190 (Jan. 18) 1919; (*b*) I. The Production of Experimental Meningitis by Direct Inoculation into the Subarachnoid Space; II. A Pathological Study of Experi-

drawal of cerebrospinal fluid in the presence of bacteremia uniformly produced meningitis. They used Bacillus lactis aerogenes for most of their work but duplicated their results with several other microorganisms. A large number of controls was employed. They first ascertained the amount of twenty-four hour broth culture which, when injected intravenously, produced no pathologic change in the control cats. Then, using half of that amount, they were able to produce fatal meningitis regularly in a large number of animals by withdrawing 1 to 2 cc. of cerebrospinal fluid within two minutes after the intravenous injection of the organisms. They found that if longer intervals were allowed to elapse between the introduction of the organisms intravenously and the removal of spinal fluid a larger amount of the broth culture had to be given by vein to cause meningitis. To obtain meningitis by intravenous injection of the organisms alone the dose had to be four to six times as large. Meningeal infection also ensued if cerebral congestion was produced immediately after the intravenous introduction of the organisms; the congestion was brought about by means of pressure on the jugular veins or by ether anesthesia deep enough to stop the circulation briefly. Lowering of the cerebrospinal fluid pressure by the intravenous injection of a hypertonic solution of sodium chloride followed by the intravenous injection of the organisms caused meningitis in several animals. The use of a hypertonic solution of dextrose, which was tried in 1 experiment, had no such effect; a hypotonic liquid, water, was also without effect. The injection of serum into the subarachnoid space, followed after several days by the intravenous injection of the organisms, resulted in meningitis in some instances. Withdrawal and replacement of cerebrospinal fluid shortly after the injection of the organisms intravenously caused meningitis; meningitis did not occur if the withdrawal and replacement were performed just before the intravenous injection. It was also possible to produce meningitis merely by introducing a needle into the subarachnoid space within two minutes after the intravenous injection. The belief that this was due to a lowering of the cerebrospinal fluid pressure was later supported by injecting india ink into the subarachnoid space of an animal and observing afterward that a considerable amount of it had leaked into the tissues surrounding the site of puncture. That this leakage did not occur in all cases is suggested by the fact that meningitis did not result when spinal fluid was removed and replaced just before the intravenous injection of the organisms. The authors per-

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mental Meningitis from Subarachnoid Inoculation; III. The Intrameningeal Virulence of Organisms; IV. The Influence of Certain Experimental Procedures upon the Production of Meningitis by Intravenous Inoculation, Monograph 12, Rockefeller Institute for Medical Research, 1920.

formed autopsies on the cats at varying intervals after the onset of meningitis. In most of them the purulent exudate and the organisms appeared first over the brain, although in a few the pus was chiefly intraspinal. This suggested that the important pathogenic factor in most cases was a lowering of the hematoencephalic barrier by reduction of the cerebrospinal fluid pressure.

Remson,[12] working with rabbits, confirmed some of the results of Weed and his co-workers. In a few of the animals killed at intervals of four, eight and sixteen hours after the intravenous injection of organisms and the performance of puncture the meningitis was localized in the region adjacent to the site of the puncture. This gave support to the suggestion that in some instances introduction of organisms into the subarachnoid space occurs at the site of the puncture. Idzumi[13] performed somewhat analogous experiments. He produced pneumococcic meningitis in some rabbits by injecting broth or serum intrathecally after the intravenous introduction of organisms. He found that dogs were resistant to the development of pneumococcic meningitis. Bull[14] was able to produce pneumococcic meningitis in some dogs by the intravenous injection of large numbers of organisms alone.

The experimental work of Flexner and Amoss[15] in producing poliomyelitis in monkeys is not entirely irrelevant. First, they determined the threshold amount of poliomyelitis virus which failed to produce poliomyelitis when injected intravenously. The virus was contained in a suspension of infected spinal cord and medulla from monkeys. By injecting intravenously only a fraction of the threshold amount of virus they were able to produce poliomyelitis provided they had injected intrathecally several hours before a small amount of horse serum, normal monkey serum, solution of sodium chloride, Ringer's solution or Locke's solution. If the removal and return of cerebrospinal fluid were carried out several hours before the intravenous injection of virus, illness did not result. The result of hemorrhage into the subarachnoid space was shown in the case of a monkey in which spinal tap accidentally produced blood-tinged fluid. Intravenous injection eighteen hours later of the same small amount of virus used in the other experiments resulted in poliomyelitis and the death of the animal.

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12. Remson, D. B.: The Role of Lumbar Puncture in the Causation of Meningitis, J. Med. **17**:115, 1936.

13. Idzumi, G.: Experimental Pneumococcus Meningitis in Rabbits and Dogs, J. Infect. Dis. **26**:373, 1920.

14. Bull, C. G.: Immunity Factors in Pneumococcus Infection in the Dog, J. Exper. Med. **24**:7, 1916.

15. Flexner, S., and Amoss, H. L.: The Relation of Meninges and Choroid Plexus to Poliomyelitic Infection, J. Exper. Med. **25**:525, 1917.

REVIEW OF CLINICAL REPORTS ON THE ASSOCIATION OF LUMBAR PUNCTURE AND MENINGITIS

There are scattered reports in the literature [16] of cases in which meningitis followed lumbar puncture. During an epidemic of meningococcic meningitis in an army camp, Wegeforth and Latham [17] performed lumbar punctures on 93 patients suspected of having meningitis, taking blood for culture at the same time. Thirty-eight had changes in the spinal fluid indicative of meningitis on the first puncture. Fifty-five had normal spinal fluid at the first puncture, and of these 6 had bacteremia. In 5 of these 6 meningitis developed; in 2 cases the meningitis was due to the pneumococcus, and in the other 3 it was caused by the meningococcus. It is inferred that meningitis did not ensue in the patients who had both normal spinal fluid and sterile blood cultures initially. The authors mentioned 1 case in which the patient had meningococcemia, lumbar puncture was not performed and meningitis did not develop. The patient in this case received antiserum intravenously twelve hours after blood was taken for culture.

Wegeforth and Latham also made an extensive review of the literature. They found numerous reports of cases of meningococcic meningitis in which the initial lumbar puncture yielded clear fluid and purulent fluid containing meningococci was present later, usually at the second tap. They mentioned, however, reported cases in which lumbar puncture was not followed by meningitis, even in the presence of bacteremia. According to these authors, most of the early writers expressed the opinion that lumbar puncture was a harmless procedure and advised that a diagnostic tap be performed early and repeated if necessary, but they themselves considered the procedure dangerous in the presence of bacteremia.

That lumbar puncture is a harmless procedure, except possibly under certain conditions, is supported by the infrequency with which complications follow its performance under ordinary circumstances. Siebert [18] reported on a series of 4,700 lumbar punctures, 1 of which was followed by meningitis and in 2 of which a needle was broken off in the tissues.

16. Symonds, C. P.: A Case of Meningitis Following Lumbar Puncture, Lancet **1**:434, 1925. Eicke, H.: Neuere Arbeiten über unangenehme Nebenwirkungen der Lumbalpunktion und ihre Vermeidung, Zentralbl. f. Haut- u. Geschlechtskr. **17**:609, 1925. Levy, I. S., and Cohen, A. E.: Pyocyaneous Meningitis After Lumbar Puncture, J. A. M. A. **85**:1968 (Dec. 19) 1925. Hammer, F.: Todesfall an Meningitis spinalis nach Lumbalpunktion, Dermat. Wchnschr. **86**:467, 1928. Netter.[8] Austrian.[9] Amoss and Eberson.[10] Weed, Wegeforth, Ayer and Felton.[11a]

17. Wegeforth, P., and Latham, J. R.: Lumbar Puncture as a Factor in the Causation of Meningitis, Am. J. M. Sc. **158**:183, 1919.

18. Siebert, H.: Erfahrungen mit Lumbalpunktionen und epiduralen Injektionen, Monatschr. f. Psychiat. u. Neurol. **52**:347, 1922.

It is extremely rare for meningitis to follow spinal anesthesia.[19] One case has been reported by Orr and Rumold,[20] that of a patient with bronchitis. They expressed the belief that the danger of meningitis as a complication of spinal anesthesia is probably increased in the case of patients with acute infections. Remson [12] commented on the case of a child with bacteremia due to the hemolytic streptococcus in which a diagnostic lumbar puncture done twenty-four hours before death yielded normal spinal fluid; autopsy showed meningitis, limited to the lower part of the spinal cord.

COMMENT

There is conclusive experimental evidence that lumbar puncture makes the meninges more susceptible to infection, as demonstrated by the production of meningitis in the presence of bacteremia. The lowered resistance in most cases is thought to be due to lowered cerebrospinal fluid pressure; in some instances it is considered to be a result of irritation and hyperemia of the meninges. That introduction of organisms may also take place at the site of puncture has been demonstrated in some cases in which the exudate was limited to the spinal cord. In such instances meningitis is thought to have occurred as a result of trauma and direct introduction of organisms from the blood stream into the subarachnoid space. In all cases bacteremia is a prerequisite to the production of meningitis. It is also significant that bacteremia alone produces meningitis if the number of organisms introduced into the blood stream is sufficiently large.

Applying these experimentally proved facts to clinical cases yields suggestive, but not entirely convincing, evidence concerning the danger of lumbar puncture. Among the cases considered in this paper are a few in which a spinal puncture preceded the onset of meningitis. In these the role of the puncture in the production of the meningitis is not entirely clear because of a multiplicity of factors. In addition to the factors operating in the production of experimental meningitis, two other possibilities have been brought out by the clinical material. Lowering of cerebrospinal fluid pressure may produce meningitis not only by drawing organisms through the blood-brain barrier but by causing a focus of infection contiguous with the meninges to rupture into the subarachnoid space. Moreover, lumbar puncture through infected tissues may introduce organisms directly into the meninges.

It is clear that whatever danger exists must often be faced, because to make a diagnosis of meningitis is frequently impossible on the basis of

19. Babcock, M. E.: Spinal Anesthesia Deaths: A Survey, Anesth. & Analg. **11**:184, 1932. Angelesco, C., and Tzovaru, S.: Quelques considérations sur la mortalité dans 120,000 rachianesthésies, Presse méd. **41**:1904, 1933.

20. Orr, T. G., and Rumold, M. J.: Meningitis Following Spinal Anesthesia, J. Kansas M. Soc. **35**:340, 1934.

symptoms and physical signs alone. This is strikingly demonstrated by the fact that the existence of meningeal infection was not recognized until after death in 17 per cent of the cases of pneumococcic meningitis reported on here. The variation in clinical signs and symptoms was especially marked in the cases of infants. The infants often had a bulging fontanel, and absence of this sign was associated in most instances with marked dehydration. Kernig and Brudzinski signs, reliable evidence of meningitis in older subjects, were sometimes lacking or equivocal in the cases of the infants. Other signs and symptoms were not constantly present. On the other hand, the presence of meningismus or the occurrence of convulsions sometimes led to the erroneous suspicion that meningitis existed.

On the basis of the data in table 7, one may say that the danger from performing lumbar puncture in the presence of bacteremia is not at all evident. These data are in contrast to experimental results.

Why is there such a discrepancy between clinical and experimental observations? One of the more likely explanations is the difference in the degree of bacteremia present at the time of lumbar puncture. In the cases of experimentally produced meningitis a specified number of bacteria was injected intravenously shortly before the withdrawal of cerebrospinal fluid. It is reasonable to suppose that clinical bacteremia is usually much less intense than that experimentally produced; information as to the number of bacterial colonies cultured was not available in many of the cases studied. But if this is so, why does meningitis occur as often as it does, whether or not lumbar puncture is performed? It is possible that the continued release of bacteria from foci of infection may exert a cumulative effect and lower the resistance of the hematoencephalic barrier. The type of organism may also be a factor, since not all bacteria gave identical experimental results. A confusing feature of a few of the cases is that blood culture and lumbar puncture were not performed at the same time, although in most instances the two procedures were carried out almost simultaneously. Also, the relation of lumbar puncture to the development of meningitis was sometimes obscured by the fact that the presence of the meningitis was often not discovered until several days after the initial withdrawal of fluid. Type-specific antiserum or one of the new chemotherapeutic agents was given to some patients, but their number was relatively small; in cases in which the patient was subjected to puncture care was taken to avoid distortion of the results by specific therapy.

CONCLUSIONS

The material studied gives evidence that in general lumbar puncture is not hazardous for the patient with bacteremia. This conclusion receives its strongest support from the fact that the incidence of menin-

gitis was no greater among patients with bacteremia who were subjected to lumbar puncture, with a yield of normal spinal fluid, than among those for whom no diagnostic tap was performed. In a few of the cases studied the performance of lumbar puncture may have been a factor in the pathogenesis of meningitis, and there are scattered reports of similar cases in the literature.

SUMMARY

Clinical observations indicate that lumbar puncture in cases of bacteremia does not cause meningitis. There may possibly be isolated exceptions.

The experimental proof of the danger of producing meningitis by means of lumbar puncture in the presence of bacteremia is reviewed.

A review of data from cases of pneumococcic meningitis and pneumococcemia is presented.

Factors in the pathogenesis of meningitis are considered, and related data are mentioned.

Dr. Edwards A. Park suggested this study. Dr. Park, Dr. Kenneth D. Blackfan, Dr. Grover F. Powers and Dr. Samuel Z. Levine made it possible to include material from the Harriet Lane Home, the Boston Children's Hospital, the New Haven General Hospital and the New York Hospital.

IMMUNITY TO TETANUS INDUCED BY COMBINED ALUM-PRECIPITATED DIPHTHERIA AND TETANUS TOXOIDS

BASED ON A STUDY OF SIXTY-FIVE ALLERGIC CHILDREN GIVEN A THIRD, OR "REPEAT," DOSE

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Ramon and his associates in their many studies on active immunization with tetanus toxoid (not alum precipitated) have demonstrated that further stimulation with toxoid results in the rapid formation of tetanus antitoxin. On this continent Sneath and Kerslake,[1] Jones and Moss,[2] Gold,[3] Hayden and Hall [4] and Hall,[5] among others, have corroborated the results of the French workers. Their studies deal largely with nonallergic adults.

In my previous study [6] on the appearance of tetanus antitoxin in the blood serum following two injections of 0.5 cc. each of combined alum-precipitated diphtheria and tetanus toxoids, special reference was made to the influence of age and the interval between injections. It was also shown that 94.6 per cent of a group of 186 allergic children attained a

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From the Children's Allergy Clinic, Mount Sinai Hospital.

F. G. Jones, of the Lilly Research Laboratories, gave technical assistance in this study.

The preparation of combined alum-precipitated diphtheria and tetanus toxoids used in this study was furnished by Eli Lilly & Co.

1. Sneath, P. A. T., and Kerslake, E. G.: Further Observations Following Administration of Tetanus Toxoid, Canad. M. A. J. **32**:132 (Feb.) 1935.

2. Jones, F. G., and Moss, J. M.: Studies on Tetanus Toxoid: II. The Response of Human Subjects to an Injection of Tetanus Toxoid or Tetanus Alum Precipitated Toxoid One Year After Immunization, J. Immunol. **33**:183 (Sept.) 1937; Combined Diphtheria Toxoid and Tetanus Toxoid, Alum Precipitated, J. Lab. & Clin. Med. **24**:512 (Feb.) 1939.

3. Gold, H.: Active Immunization of Allergic Individuals Against Tetanus by Means of Tetanus Toxoid, Alum Precipitated Refined, J. Allergy **9**:545 (Sept.) 1938.

4. Hayden, R., and Hall, W. W.: Active Immunization Against Tetanus, Using Alum Precipitated Tetanus Toxoid, U. S. Nav. M. Bull. **36**:524 (Oct.) 1938.

5. Hall, W. W.: Tetanus Toxoid Immunization in the United States Navy, Ann. Int. Med. **14**:565 (Oct.) 1940.

6. Peshkin, M. M.: Immunity to Tetanus Induced by Combined Alum-Precipitated Diphtheria and Tetanus Toxoids, Based on a Study of One Hundred and Eighty-Six Allergic Children, Am. J. Dis. Child. **62**:9 (July) 1941.

protective level of tetanus antitoxin, the critical level being placed at 0.01 American unit of antitoxin per cubic centimeter of blood. The remaining 5.4 per cent had an inadequate level of antitoxin (0.003 unit per cubic centimeter of serum).

In this communication I am reporting the results of a study to determine the effect on the tetanus antitoxin response and the duration of immunity of a third, or "repeat," injection of 0.5 cc. of the combined alum-precipitated toxoids given to 65 of the 186 children used in the first study. Nine of these 65 children had failed to attain adequate immunity after two doses of the combined alum-precipitated toxoids.

MATERIAL AND METHODS

A total of 332 tetanus antitoxin titrations were done on the blood serums obtained from the 65 allergic children after the "repeat" injection of 0.5 cc. of the combined alum-precipitated toxoids, administered from three to fifteen months after completion of the basic immunization with two 0.5 cc. doses of the toxoids. One hundred and fifty-three titrations had been made after the first two injections.

TETANUS ANTITOXIN TITERS AFTER THE SECOND AND AFTER THE THIRD DOSE OF COMBINED ALUM-PRECIPITATED TOXOIDS

Examination of the data revealed that for 34 patients titers determined after the second dose of combined toxoids were available for study with the 87 obtained at intervals of from seven days to one year after the third dose. The antitoxin value after the third dose of the combined toxoids was higher in 74 of the 87 instances, lower in 4 and the same in 9. After the third dose the average increase in the antitoxin value was 15 times more and the average decrease 4 times less than the corresponding titers after the second dose.

From the data it was deduced that when the initial tests were done within two months of giving the combined toxoids and the comparative tests showed the antitoxin values to be higher, the same or even lower after the respective third and second doses, then the tests performed from seven to twelve months later revealed not only that the drop of the titer was retarded after the third dose but that the antitoxin values were also higher.

ANTITOXIN TITER OBTAINED WITHIN ONE MONTH OF THE REPEAT DOSE OF COMBINED TOXOIDS AND THE CONTROL TITER

Data with which to determine the effect of the third dose of toxoid on the antitoxin response, with reference to the antitoxin titer obtained

after the second and immediately preceding the third dose of combined toxoids, were available for 58 patients. These patients were divided into three groups. Group 1 consisted of 9 children who failed to attain adequate immunity (an antitoxin level of 0.01 unit per cubic centimeter of serum) after the second dose of toxoid. Following the third dose of toxoid the titers ranged from 0.017 to 1 unit of antitoxin, or an average of 0.296 unit per patient. The increase in titer was from 6 to 33 times, or an average of 99 times, more than the control titer of 0.003 unit (inadequate immunity).

Group 2 consisted of 21 patients who had an adequate antitoxin level soon after the second dose of toxoid but whose titers some months later dropped to the level of 0.003 unit per cubic centimeter of serum. After the third dose of toxoid the titers ranged from 0.1 to 5 units of antitoxin, or an average of 0.876 unit per patient. The increase in titer was from 33 to 1,667 times, or an average of 292 times, more than the control titer of 0.003 unit.

Group 3 consisted of 28 patients who had an adequate antitoxin response soon after the second dose of toxoid but whose subsequent titers, obtained some months later, though lowered, remained above the critical level of protection against tetanus. For 1 patient the control titer and the titer following the third dose of toxoid remained the same—0.05 unit of antitoxin. After the third dose of toxoid the titers of the remaining 27 patients ranged from 0.2 to 4 units of antitoxin, or an average titer of 1.166 units. The increase in titer ranged from 5 to 235 times, or an average of 33 times more than the average control titer of 0.035 unit of antitoxin.

For 5 of the children in the three groups antitoxin levels were also determined within thirty days of a fourth dose of 0.5 cc. of combined toxoids. The average antitoxin level of these 5 children after the second, third and fourth doses was 0.01, 0.134 and 0.23 unit, respectively. A fifth dose administered to 1 of these children resulted in an antitoxin titer of only 0.5 unit of antitoxin.

An analysis of the foregoing figures and of the other data indicated that the antitoxin values obtained within one month after the administration of three or more doses of the combined toxoids varied according to the antitoxin level present immediately preceding the repeat injection and the nature of the immunity mechanism. When the titer was always maintained at the inadequate level (0.003 unit of antitoxin) after two doses of toxoid then the lowest average titer (0.296 unit) followed a third dose. When the titer dropped to the inadequate level subsequent to being adequate (0.01 unit or more of antitoxin) after two doses of toxoid then the average titer following a third dose rose to 0.876 unit

of antitoxin. When the titer was always maintained at the adequate level after two doses of toxoid then the titer following a third dose reached the highest antitoxin value, the average being 1.116 units of antitoxin. Moreover, for 3 of 5 children to whom it was desirable to administer a fourth or fifth dose of the combined toxoids the antitoxin levels tended to become higher, but only within certain limits (0.5 unit of antitoxin or less).

TIME OF OCCURRENCE OF THE MAXIMUM ANTITOXIN RESPONSE

To determine the maximum antitoxin response following the third dose of toxoid only the 58 patients for whom two or more tests were done within one hundred days of the injection were selected for study. The antitoxin level of 1 patient four days after the repeat dose of combined toxoids was 0.017 unit per cubic centimeter of serum, while on the fourteenth day after administration of the toxoids the titer was 0.2 unit of antitoxin. Tests performed five days after the repeat dose showed titers of 0.017 and 0.1 unit of antitoxin for 2 other children, while the maximum titer within one month of giving the toxoids was 0.5 unit of antitoxin for each child.

Of 37 patients tested seven days after the third dose, only 1 had 0.003 unit of antitoxin per cubic centimeter of serum. Thirty days later this patient's titer had increased to 0.05 unit of antitoxin. Comparative tests done on another patient showed 0.5 unit of antitoxin on the seventh day and 0.003 unit on the fourth day. The remaining 35 patients showed the following antitoxin levels: 0.01 unit, 1 child; 0.05 unit, 1 child; 0.1 unit, 3 children; 0.2 unit, 5 children; 0.5 unit, 8 children; 1 unit, 8 children; 2 units, 6 children; 3 units, 2 children, and 5 units, 1 child. The average antitoxin titer for the 37 children tested seven days after the toxoid was given was 1 unit. These results indicated that adequate tetanus antitoxin levels were attained from five to seven days after the injection of a third dose of 0.5 cc. of the combined toxoids by practically all of the children treated. The antitoxin level ranged from 0.1 to 5 units in 90 per cent of the children tested. For the majority of the patients the antitoxin titer was at its maximum seven days after the administration of the combined toxoids.

All 14 of the children first tested from fourteen to twenty-one days after receiving the third dose of combined toxoids showed maximum and adequate antitoxin responses ranging from 0.1 to 2 units per cubic centimeter of serum, with an average of 0.686 unit.

Three of the 4 patients first tested within one month of receiving the third dose of toxoid showed an antitoxin level between 0.2 and 4 units per cubic centimeter of serum. The remaining patient had a titer of only 0.017 unit of antitoxin. The average antitoxin titer of 1.179 unit

for this group of children is obviously too high to be representative, since the number of patients was so few. The expected average should be less than that recorded for the preceding group of children.

All of the foregoing observations are largely confirmed by the results recorded in a preceding paper, of a similar study on a smaller comparable group of 30 children who received only two doses of 0.5 cc. each of the combined toxoids. However, in addition to the higher antitoxin values obtained after a third dose of toxoid for the children comprising this series, adequate titers were also attained by all of the children within one month and for the majority the antitoxin titer was at its maximum level on the seventh day after the preparation of combined toxoids was administered.

RATE OF DECLINE OF THE ANTITOXIN TITER FROM AN ADEQUATE TO AN INADEQUATE LEVEL

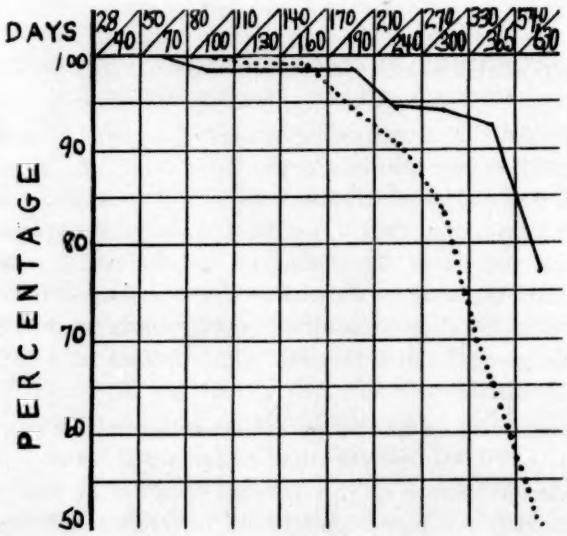
All of the 65 children comprising this series acquired adequate tetanus antitoxin levels at least within one month of the third, or repeat, dose of combined toxoids. The relation between the percentage of children who showed a drop of antitoxin titer from an adequate to an inadequate level and the number of days required for the titer to drop to the inadequate level is shown in the chart. For purposes of contrast, there is also shown in the chart an antitoxin curve constructed from data for a comparable group of 102 children who received only two doses of combined toxoids.

It was previously stated that an antitoxin titer which dropped to the inadequate level (0.003 unit per cubic centimeter of serum) after a dose of toxoid was maintained at this residual level for at least two years. For this reason it was found unnecessary to retest all of these children within the period this study covered. Nevertheless, retests on a number of these children were carried out in order to detect any sharp rise of antitoxin titer which might possibly follow a "natural" stimulus. Perusal of the results of the 332 tests done after the third injection revealed that the titers of all except 1 child fell progressively from their initial maximum levels. For this child the maximum initial titer was 0.2 unit of antitoxin seven days after the third dose was given. Eight months later the titer dropped to 0.017 unit of antitoxin, and one year later it rose to 0.1 unit (and the same value was obtained on rechecking the serum). It is extremely difficult to explain this result satisfactorily on the basis of possible technical error, a plausible argument when applied to minor changes in titer but not to an increase in titer six times greater than the control. The idea that this increase in titer may have followed a natural stimulus cannot be discarded. However, only retests repeated over a considerable period on actively immunized children known to maintain

residual titers of from 0.003 to 0.017 unit of antitoxin will give definite information on this subject.

An analysis to determine the influence on the antitoxin level of the interval between the injection of the second and the third dose of combined toxoids was not made because the 9 children who were given injections at intervals of from two to four months were too few to be comparable with the 56 children given injections at longer intervals.

Examination of the chart shows that for the first three months after the third dose of toxoid was given 100 per cent of the 65 children maintained adequate immunity. Four and six months after receiving the combined toxoids 98.4 per cent of the children had adequate antitoxin



Percentages of 65 allergic children (solid line) who had achieved adequate immunity to tetanus (0.01 unit or more of antitoxin per cubic centimeter of blood serum) within one month after a third, or "repeat," dose of combined alum-precipitated diphtheria and tetanus toxoids and of a group of 102 allergic children (dotted line) who had adequate antitoxin levels after two doses of the combined toxoids who maintained adequate antitoxin titers for a varying number of days after immunization.

levels. One and one and one-half years after administration of the combined toxoids 92.3 and 76.7 per cent of the children, respectively, still had immunity. In contrast, the percentages of the 102 children who maintained adequate immunity for corresponding periods after the second dose of toxoid were 100, 99.4 and 94.6, 65 and 50, respectively. The 1 child whose titers showed a drop to the inadequate antitoxin level three months after receiving the third dose of toxoid also failed to attain adequate immunity after the second dose and so must be

regarded as being refractory to active immunization with three doses. However, two months after a fifth dose the antitoxin level rose to 0.5 unit per cubic centimeter of serum.

It is obvious from the curves in the chart that a definitely greater percentage of the children who received a third dose of combined toxoids had adequate immunity to tetanus one and one-half years later than of those given two doses of toxoid.

Maximum Tetanus Antitoxin Titer of Allergic Children and Titers Obtained Less Than One Year, When the Titer Dropped to 0.003 Unit of Antitoxin per Cubic Centimeters of Blood Serum, and One Year After the Second and Third Injections of Combined Alum-Precipitated Diphtheria and Tetanus Toxoids *

Maximum Antitoxin Titer	Patients		Antitoxin Titer, Units per Cc. of Serum, After Injection of Toxoid															
			Less Than One Year		One Year													
			0.003 †		0.003		0.01 †		0.05		0.1		0.2		0.5		0.01 or More	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
After Second Dose																		
0.01 ‡	1	1	1	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.025	1	1	1	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.05	6	7	4	66	1	17	1	17	0	0	0	0	0	0	0	0	1	17
0.1	11	14	5	46	3	27	1	9	2	18	0	0	0	0	0	0	3	27
0.2	27	33	3	11	2	7	19	71	2	7	1	4	0	0	0	0	22	81
0.5	16	20	1	6	1	6	6	38	5	31	1	6	2	13	0	0	14	87
1.0 or more	19	24	0	0	2	10.5	5	26	4	21	2	10.5	6	32	0	0	17	89
Total	81	100	15	18.5	9	11.1	32	39.5	13	16.1	4	4.9	8	9.8	0	0	57	70
After Third Dose																		
0.01 ‡	1	2	1	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.1	2	4	1	50	0	0	1	50	0	0	0	0	0	0	0	0	1	50
0.2	9	17	0	0	2	22	5	55	1	11	1	11	0	0	0	0	7	78
0.5	18	35	0	0	0	0	8	45	4	22	6	33	0	0	0	0	18	100
1.0 or more	22	42	0	0	0	0	6	27	2	9	5	23	7	32	2	9	22	100
Total	52	100	2	3.8	2	3.8	20	38.5	7	13.5	12	23.1	7	13.5	2	3.8	48	92

* Data are included only for those children for whom titrations were performed within forty days of the injection of toxoid. Data for the 81 children given two doses were obtained in a previous study.[6]

† Data for patients with an antitoxin titer of 0.003 unit less than one year after immunization are included because such titers persist at this level for at least two years.

‡ Patients with an antitoxin level of 0.017 unit are grouped with those having a titer of 0.01 unit.

INITIAL MAXIMUM ADEQUATE ANTITOXIN LEVEL AND LEVEL ONE YEAR AND LESS THAN ONE YEAR AFTER THE SECOND AND THIRD DOSES OF COMBINED TOXOIDS

Fifty-two of the 65 children comprising this series were available for retesting one year after receiving a third dose of toxoid. In the table the initial adequate antitoxin titers (when more than one titer was obtained within one month of the administration of toxoid only the maximum titer was recorded) and the titers obtained less than one year (when the titer dropped to the inadequate level) and one year after administration of the combined toxoids are compared. The table

also gives data for a comparable group of 81 children who received only two doses of toxoid.

The table shows that 18.5 per cent of the 81 children who received two doses of toxoid and 3.8 per cent of the 52 who received three doses showed a drop in titer from a maximum initial adequate to an inadequate level less than one year after receiving the last dose of combined toxoids. Only the children given two doses who showed an initial level of 1 unit of antitoxin or more and those given three doses who showed an initial level of 0.2 unit or more did not show a drop in titer to the inadequate level less than one year after the last dose of toxoid.

At the end of one year 9 children, or 11.1 per cent of the 81 who received two doses of toxoid, as compared with 2, or 3.8 per cent, of the 52 who received three doses, showed a drop in titer to the inadequate level. However, 8.5 per cent of the children of the former group who had an initial antitoxin level of 0.5 unit or higher showed a drop in titer to the inadequate level at the end of one year, while all the children of the latter group maintained an adequate titer. Moreover, 40 per cent of the children given three doses as compared with only 16 per cent of the children given two doses had 0.1 unit of antitoxin or more per cubic centimeter of serum at the end of one year. This ratio of 2.5 : 1 is largely due to the fact that 77 per cent of the former group as compared with 30 per cent of the latter group had maximum initial titers of from 0.5 to 1 unit or more of antitoxin.

Thus, it can be observed that the antitoxin titer of 30 per cent of the 81 allergic children dropped from an adequate to an inadequate level one year or less than one year after the administration of two doses of combined toxoids and that only 8 per cent of the 52 allergic children given three doses had an inadequate titer.

Not only did a higher percentage of the children given three doses of combined toxoids than of those given two doses attain the highest antitoxin levels after the third dose, but one year later 92 per cent of them showed adequate antitoxin levels (up to 0.5 unit of antitoxin per cubic centimeter of serum) as compared with 70 per cent of those given two doses who showed adequate levels (up to 0.2 unit of antitoxin).

REACTION AND SENSITIVITY

Of 65 children approximately 25 per cent had local reactions of various degrees after the third injection of combined toxoids. The reactions were similar to those described in the preceding communication. No hemorrhagic reactions followed the third dose. In only 2 instances were local reactions considered notable. One child had a slight and another a marked local reaction and some hours after the injection of the combined toxoids both children experienced an elevation of tem-

perature to 103 F., which lasted for about one day. Thus, the incidence of febrile reactions of 3 per cent in this group of 65 children is greater than the incidence of 1 per cent in the group of 186 children given two doses of toxoid, who were reported on in the previous study.

Five of the 65 children were given a fourth dose, and 1 of these 5 received a fifth dose of combined toxoids. All 5 children had slight to moderate local reactions. However, 1 of these 5 children had an elevation of temperature for one day only after the third dose of combined toxoids and was included in computing the foregoing incidence of 3 per cent of febrile reactions.

Not 1 of the 65 allergic children showed a general reaction simulating any of the known allergic syndromes after a third injection of combined alum-precipitated diphtheria and tetanus toxoids. The scratch test performed on 36 of the children with the undiluted combined toxoids resulted in negative reactions, immediate and delayed. On 31 of these children the tests were performed from one to two years after and on the remainder from three to six months after the repeat dose of toxoid. It is probable that a positive reaction would have been elicited from some of the former group of children if the tests had been performed within four months of the administration of the repeat dose. However, in view of the fact that negative cutaneous reactions were obtained one to two years after the third injection of the combined alum-precipitated diphtheria and tetanus toxoids, a fourth injection would be justified if one accepts a negative cutaneous reaction to the toxoid preparation as a criterion of insensitivity.

Local and general reactions following the subcutaneous injection of the combined toxoids are fully discussed in the previous communication.

COMMENT

The importance of the role of allergy in the establishment of immunity was more vividly evident throughout this study than it was in the preceding one. When a child has had two injections of combined toxoids a better state of preparation is established than after one injection. This state of preparation is a most important feature of active immunization. Within certain limits, repeated injections are, on this account, more effective in raising the antibody titer to a higher level than two injections and so insuring protection of the patient from tetanus. The capacity to respond in such a manner to a third dose is evidenced by the results obtained with the 65 children comprising this series.

The fact that allergic children were the subjects under treatment and that the preparation of combined alum-precipitated diphtheria and tetanus toxoids does contain traces of beef broth and peptone as well as

bacterial substances should be borne in mind. Naturally, the question of sensitization to these substances was closely studied. Thus far, in the active immunization of 186 allergic children who have had two to five doses of combined toxoids, for a total of 443 injections, no untoward allergic reaction, such as urticaria or asthma, or cutaneous sensitivity to the toxoid preparation has been encountered. The longest interval between the injections was fifteen months. Whether or not employing a longer interval will result in allergic reactions, general or cutaneous, is under investigation.

SUMMARY AND CONCLUSIONS

From three to fifteen months after the completion of primary immunization with two 0.5 cc. doses of combined alum-precipitated diphtheria and tetanus toxoids (of a toxicity of 30,000 minimum lethal doses per cubic centimeter), 65 allergic children were given a third, or repeat, dose of 0.5 cc. Antitoxin levels were determined at various periods after the second and after the third dose of the combined toxoids, and totals of 153 and 332 tetanus antitoxin titrations, respectively, were performed.

The incidence of local reactions both after the third and after the first two injections was about 25 per cent. An elevation of temperature lasting about one day followed administration of the third dose to 3 per cent of the children, as compared with an incidence of 1 per cent among those given two doses.

No allergic reactions, such as urticaria or asthma, were encountered.

From three months to two years after the repeat injection, negative reactions to scratch tests with undiluted combined alum-precipitated diphtheria and tetanus toxoids were obtained for 36 children.

Adequate tetanus antitoxin titers (0.01 unit or more of antitoxin per cubic centimeter of blood serum) were attained by all children within one month, and for the majority the titer was at its maximum level on the seventh day after a repeat dose of the combined toxoids. After a second dose adequate immunity was not attained by all of the children.

For the large majority of children the antitoxin values obtained within one month of the administration of three doses of the combined toxoids varied according to the antitoxin level present immediately preceding the repeat dose. For example, the children were grouped according to antitoxin control titers as follows: (1) those who always failed to show more than 0.003 unit, (2) those who had a level of 0.003 unit subsequent to having higher values and (3) those who had an average level of 0.035 unit per child subsequent to having higher average values. After the third dose the average antitoxin titer per patient of the three groups increased to 0.296, 0.876 and 1.166 units per cubic centimeter of serum, respectively.

Comparison of the initial maximum antitoxin levels and the corresponding titers one month and one year after administration of the third and the second dose of combined toxoids revealed not only that the percentage of children attaining the highest antitoxin levels (0.5 to 1 unit of antitoxin or more) within one month of receiving the third dose was significantly higher than of those receiving two doses (77 as compared to 30 per cent) but that one year later the ratio between the patients of the two groups who showed an antitoxin titer of 0.1 unit or more was 2.5 : 1 (40 and 16 per cent, respectively).

The percentages of children with adequate immunity one and one and one-half years after receiving the third dose of combined toxoids were definitely higher (92 and 77) than the percentages (65 and 50) obtained for a comparable group of children after a second dose.

Thus, it can be concluded that the injection of a third, or repeat, dose of combined alum-precipitated diphtheria and tetanus toxoids into allergic children was followed in all instances by an adequate tetanus antitoxin titer, which was higher and lasted for a much longer period than that which followed the second injection, even though the corresponding titer obtained within one month of the third injection was the same or less. Moreover, there appears to be a limit beyond which repeated injections fail to increase the titer.

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DEPRIVATION OF PLACENTAL BLOOD AS A CAUSE OF IRON DEFICIENCY IN INFANTS

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When the umbilical cord is clamped immediately after birth, over 100 cc. of blood can usually be obtained from the placental end of the cord.[1] This blood normally flows into the infant if clamping is delayed until the placenta begins to descend into the vagina.[2] During the neonatal period the infant's total blood volume is about 10 per cent of the body weight,[3] and the average weight at birth is about 3.2 Kg.; therefore it is possible that the blood contained in the placenta and its surface vessels is equivalent to a third of the blood volume of the newborn infant. We have shown previously that depriving the infant of the placental blood results in a significant decrease in the erythrocyte count and the hemoglobin content of the blood and an increase in the reticulocytes during the first week of life.[2c] Further observations have indicated that failure of the infant to receive such blood may lead to a deficiency of iron during the first year of life.

The infant is largely dependent on the supply of iron present at birth for growth and for the formation of hemoglobin during the first six

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months of life. The amount of iron obtained from the diet over this period, and even up to the end of the first year, is minimal.[4] The iron reserve of the infant at birth is contained in the circulating hemoglobin and, to a lesser extent, in the tissues. The iron liberated during the physiologic destruction of blood is stored and becomes available for reutilization. At the end of six months the total iron content of the infant is about the same as at birth,[5] but the hemoglobin content per hundred cubic centimeters of blood is reduced almost to half the amount present at birth, and the reserve of iron in the tissues is decreased.[6]

The total iron content of the newborn infant averages 350 mg.,[5a] and we estimate (table 1) that about 236 mg. of the iron is contained in the circulating hemoglobin. Probably somewhat over half of the remaining iron is present in the tissues in a free form. At 6 months of age the total amount of iron in the circulating hemoglobin is about the same as at birth. Therefore the amount of iron made available through the destruction of blood should equal the amount of iron needed for the formation of hemoglobin during the first six months of life. If one considers the amount of parenchymal iron needed for growth and the fact that there is a negative iron balance of 50 to 75 mg. during the first two months of life,[4b] it seems likely that the infant's reserve of iron in the tissues is largely depleted by the end of six months.

It is apparent, then, that a decrease in the total amount of iron present at birth could result in a state of iron deficiency during later infancy. Two possible causes of reduction in the iron content of the newborn infant are: (*a*) iron deficiency in the mother [7] and (*b*) deprivation of the infant of placental blood.[2c] Strauss [8] and Blackfan and Diamond [9] have reported that in infants born of mothers with anemia due to iron deficiency, anemia develops during the first year. No consideration has been given previously to the possible importance of deprivation of

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placental blood as a cause of anemia in infancy. Such an etiologic relation is suggested by certain calculations from data in the literature (table 1).

The iron content of the placental blood may be calculated as follows:

Average amount of blood in placenta	105 cc.
Hemoglobin content of placental blood	16 Gm. per 100 cc.
Iron content of placental blood	56.3 mg.

The theoretic effect of depriving the infant of the iron of the placental blood may be indicated as follows:

Age 6 months:

Total iron content of hemoglobin of infant's blood plus placental blood 235 mg. (equivalent to iron content of 12 Gm. of hemoglobin per 100 cc. of blood)

TABLE 1.—*Total Amount of Iron in Circulating Hemoglobin During Infancy*

	Average Weight, Kg.	Blood Volume, Percentage of Weight	Hemoglobin Content, Gm. per 100 Cc. of Blood	Total Amount of Iron in Circulating Hemoglobin,* Mg.
At birth	3.2	10 [3]	22 [2c]	236
At 6 months of age	6.5	9 †	12	235
At 9 months of age	8.0	9 †	12	290

* Hemoglobin is 0.335 per cent iron. The total amount of iron in circulating hemoglobin is equal to the body weight (in grams) × blood volume (in percentage of body weight) × hemoglobin content per cubic centimeter × 0.00335.

† Bakwin, H., and Rivkin, H.: The estimation of the Volume of Blood in Normal Infants and in Infants with Severe Malnutrition, Am. J. Dis. Child. **27**: 340 (April) 1924.

Result of deprivation of iron in placental blood $\frac{235 - 56.3}{235} \times 12 = 9.1$ Gm. of hemoglobin per 100 cc. of blood

Age 9 months:

Total iron content of hemoglobin of infant's blood plus placental blood 290 mg. (equivalent to iron content of 12 Gm. of hemoglobin per 100 cc. of blood)

Result of deprivation of iron in placental blood $\frac{290 - 56.3}{290} \times 12 = 9.7$ Gm. of hemoglobin per 100 cc. of blood

One may assume that the average amount of blood lost to the infant by early clamping of the cord is 105 cc.[2b] Since the hemoglobin content of cord blood is about 16 Gm. per hundred cubic centimeters,[2c] by immediate clamping of the cord the infant is deprived of 56.3 mg. of iron. If it is true that the infant is dependent on the iron present at birth for the normal formation of hemoglobin later, the loss of this much iron will result in a lowering of the hemoglobin content of the blood at 6 months of age from 12 to 9.1 Gm. per hundred cubic centimeters and at 9 months of age from 12 to 9.7 Gm.

MATERIAL AND METHODS

In order to test this hypothesis studies were made at the ages of 8 to 10 months on 28 of the infants from a previous series.[2c] Erythrocyte counts were made with equipment certified by the United States Bureau of Standards and hemoglobin determinations with a Sahli-Hellige apparatus, which was calibrated by the oxygen capacity technic. All samples of blood were obtained from the heel. The investigator (E. E. W.) who visited the infants' homes to obtain the hematologic data did not know which of the babies had been deprived of placental blood at birth.

RESULTS

The umbilical cords of 15 of the infants studied had been clamped immediately after birth (group 1); clamping of the cords of the other 13 infants had been delayed until the placenta had begun to descend into the vagina (group 2). Data for the two groups of infants are recorded in tables 2 and 3.

Before we discuss the blood values, mention should be made of the economic status, the type of feeding and the occurrence of infections, because these factors may play a role in the production of iron deficiency. All of the infants came from families of a low income group. Living and home conditions, for the most part, were poor. The information about feeding, obtained from the mothers, was inadequate and uncertain. Eight infants of group 1 and 9 of group 2 had been breast fed, at least partially, for varying lengths of time. Nearly all were receiving some carrots, spinach and other green vegetables. The general health of the babies was surprisingly good, even though they lived in homes which were obviously poverty stricken. No splenic or hepatic enlargement was observed. Slight to moderate cervical adenopathy was present in 9 infants of group 1 and in 5 of group 2. Many of the babies had had colds, but there was no history of serious illness for any subject included in this study. One infant had been sick for three or four weeks, with cough, fever and rales throughout the chest. For this reason he was omitted from the series. There seemed to be no consistent difference in the factors operative in the two groups which might predispose the infants to iron deficiency anemia.

As may be seen from the tables, the hemoglobin values for the mothers at the time of delivery were all within normal limits. So far as we know, none had received iron therapy during pregnancy. The average weights of the two groups of infants were about the same at birth, whereas at 8 to 10 months of age the average weight of the babies in group 1 was slightly greater than that of the infants in group 2.

The blood values recorded for the first week of life are averages of four determinations made during that week. For group 1 the average values were: 5,430,000 red corpuscles per cubic millimeter of blood and 19.4 Gm. of hemoglobin per hundred cubic centimeters, as compared with

6,200,000 red corpuscles and 22.8 Gm. of hemoglobin for group 2. This difference is about the same as that reported previously [2c] for the larger series which included these infants. At 8 to 10 months of age the average

TABLE 2.—*Blood Values for Infants Whose Umbilical Cords Were Clamped Immediately After Birth (Group 1)*

		First Week of Life			8-10 Months of Age				
Case No.*; Race, Sex	Hemoglobin Content of Maternal Blood,† Gm. per 100 Cc.	Weight, Gm.	Red Blood Corpuscles, Millions per Cu. Mm.	Hemoglobin Content, Gm. per 100 Cc.	Age, Week	Weight, Gm.	Red Blood Corpuscles, Millions per Cu. Mm.	Hemoglobin Content, Gm. per 100 Cc.	Mean Corpuscular Hemoglobin, Micromicrograms
10 C M	13.3	2,736	5.10	18.6	34	7,938	4.78	8.2	17.1
1 W M	14.0	3,969	4.74	17.3	35	9,073	4.68	12.0	25.6
2 C F	12.0	3,686	4.37	15.7	35	8,165	3.38‡	10.5	31.1
22 W M	11.5	3,601	6.28	22.0	36	11,341	6.06	10.5	17.3
5 C M	12.5	2,814	5.27	18.7	36	7,485	4.27	7.4	17.3
7 C F	11.0	3,388	5.03	18.1	37	7,258	5.52	10.0	18.1
8 C F	12.0	3,657	5.60	18.3	37	8,335	4.47	9.8	20.9
6 C F	11.5	3,246	5.97	21.6	38	7,485	5.31	11.8	22.2
15 C M	13.0	3,218	5.31	19.7	38	8,619	5.05	8.0	15.8
11 W F	12.0	4,210	5.66	21.0	38	9,073	4.53	13.5	29.8
13 W M	12.5	3,445	5.82	19.3	38	9,526	5.41	11.9	22.0
16 W F	12.8	3,112	5.81	21.0	39	8,165	5.35	12.8	23.9
20 C F	14.5	2,885	4.54	18.0	40	7,258	4.14	11.5	27.8
24 W M	13.5	4,082	6.17	21.0	41	9,299	6.99	12.5	17.9
17 W M	14.0	3,111	5.77	20.9	45	7,485	5.99	12.0	20.0
Average	12.7	3,411	5.43	19.4	38	8,434	5.06	10.8	21.8
Standard Deviation (σ)			±0.56	± 1.8			±0.87	± 1.9	± 4.6

* Number used in previous communication.[2c]
† Determined on blood obtained at delivery.
‡ The infant had no abnormality which would explain this unusually low count.

blood values for the 15 infants whose cords were tied immediately (group 1) were: red blood corpuscles, 5,060,000 per cubic millimeter; hemoglobin content, 10.8 Gm. per hundred cubic centimeters, and mean

corpuscular hemoglobin,[10] 21.8 micromicrograms. For the 13 infants of group 2 the average values were: red blood corpuscles, 4,450,000 per cubic millimeter; hemoglobin content, 11.9 Gm. per hundred cubic centimeters, and mean corpuscular hemoglobin, 27.0 micromicrograms. Four

TABLE 3.—*Blood Values for Infants Whose Umbilical Cords Were Not Clamped Until the Placenta Began to Descend Into the Vagina (Group 2)*

		First Week of Life			8-10 Months of Age				
Case No.*; Race, Sex	Hemoglobin Content of Maternal Blood,† Gm. per 100 Cc.	Weight, Gm.	Red Blood Corpuscles, Millions per Cu. Mm.	Hemoglobin Content, Gm. per 100 Cc.	Age, Week	Weight, Gm.	Red Blood Corpuscles, Millions per Cu. Mm.	Hemoglobin Content, Gm. per 100 Cc.	Mean Corpuscular Hemoglobin, Micromicrograms
3D W M	14.0	3,218	6.37	22.5	35	7,031	4.29	13.5	31.5
5D C M	12.5	2,353	6.69	25.3	35	7,712	4.92	10.0	20.3
2D W F	14.3	3,020	5.52	22.0	36	9,073	4.45	11.8	26.5
4D C M	11.8	3,537	6.15	22.3	36	7,939	4.64	10.8	23.3
6D W F	11.5	3,331	6.06	25.1	36	8,392	4.35	11.8	27.1
2D W M	14.5	2,254	6.00	22.8	37	5,841	4.98	10.5	21.1
25D W M	12.5	3,927	7.06	23.5	38	7,712	3.94	12.0	30.5
18D C M	12.5	3,667	6.77	24.0	38	9,526	4.75	12.5	26.3
22D W F	13.8	3,374	6.11	20.8	38	7,938	4.10	14.8	36.1
17D W F	13.5	4,196	5.53	21.1	39	8,278	4.16	12.5	30.0
21D W F	12.5	4,132	5.93	22.2	39	9,073	4.38	10.5	24.0
8D C F	12.0	3,012	6.65	24.7	41	7,258	4.55	11.6	25.0
28D W F	10.5	3,175	5.24	20.5	42	7,045	4.29	12.3	28.7
Average	12.8	3,369	6.20	22.8	38	7,909	4.45	11.9	27.0
Standard Deviation (σ)			±0.52	± 1.5			±0.30	± 1.3	± 4.3

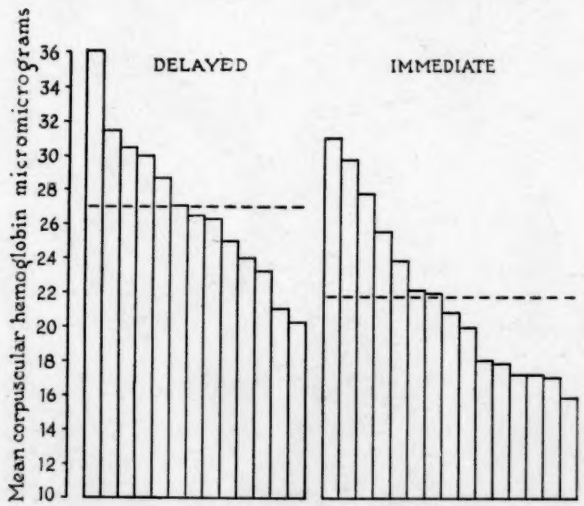
* Number used in previous communication.[2c]
† Determined on blood obtained at delivery.

infants in group 1 had a hemoglobin content below 10 Gm. per hundred cubic centimeters of blood, whereas that of none fell below this level in group 2.

10. The mean corpuscular hemoglobin, in micromicrograms, equals

$$\frac{\text{hemoglobin content (grams per thousand cubic centimeters)}}{\text{red blood cells (millions per cubic millimeter)}}.$$

Although the differences in the average erythrocyte counts and hemoglobin values for the two groups are not highly significant in themselves, it should be noted that for group 1 the average erythrocyte count is higher and the average hemoglobin value lower than for group 2. An increase in the erythrocyte count accompanied by a decrease in the hemoglobin content has been observed for rats fed milk diets.[11] This is a sign of iron deficiency. The ratio of the hemoglobin content of the blood to the erythrocyte count is expressed as the mean corpuscular hemoglobin. The difference between the mean corpuscular hemoglobin of the two groups of infants (illustrated graphically in the figure) is statistically significant. It means that there was a reduction in the mean corpuscular volume and/or the mean corpuscular hemoglobin concentra-



Mean corpuscular hemoglobin of 15 infants whose umbilical cords were clamped immediately after birth and of 13 infants whose cords were not clamped until the placenta began to descend into the vagina. The broken lines indicate the average value for each group.

tion of the infants whose cords were clamped immediately. Such a change in the corpuscles occurs in iron deficiency anemia. Further studies are being made in an attempt to obtain more detailed information

11. Alt, H. L.: Experimental Goat's Milk Anemia, Proc. Soc. Exper. Biol. & Med. **33**:48 (Oct.) 1935. Parsons, L. G.; Hickmans, E. M., and Finch, E.: Studies in Anaemia of Infancy and Childhood: XI. The Effect of Iron Deficient Diets on the Size of the Red Blood Cells in Rats and in the Production of Microcytic Hypochromic Anaemia in Their Offspring; a Contribution to the Study of Congenital Iron Deficiency in the Human Infant, Arch. Dis. Childhood **12**:369 (Dec.) 1937.

on the relation of the amount of iron present at birth to anemia during later infancy.

SUMMARY

Infants whose umbilical cords were clamped immediately after birth had a lower mean corpuscular hemoglobin at 8 to 10 months of age than those whose cords were clamped after the placenta began to descend into the vagina. It is therefore suggested that deprivation of the infant of the placental blood by early clamping of the cord may lead to an iron deficiency during the first year of life.

FAT EXCRETION OF PREMATURE INFANTS

I. EFFECT ON FECAL FAT OF DECREASING FAT INTAKE

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In a previous study of the nitrogen metabolism of premature infants,[1] attention was called to the defective ability of such infants to absorb fat. This defect had been noted earlier by Rubner and Langstein,[2] by Muhl [3] and by Holt and his co-workers [4] and was considered by Ylppö [5] to be a factor contributing to the tendency for rickets to develop in premature infants. In a subsequent study of the energy exchange of premature infants,[6] the loss of calories in the feces was found to be two to three times that reported for full term infants. It was suggested that the use for premature infants of a feeding mixture from which

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From the New York Hospital and the Department of Pediatrics, Cornell University Medical College.

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1. Gordon, H. H.; Levine, S. Z.; Wheatley, M. A., and Marples, E.: Respiratory Metabolism in Infancy and in Childhood: XX. The Nitrogen Metabolism in Premature Infants; Comparative Study of Human Milk and Cow's Milk, Am. J. Dis. Child. **54**:1030 (Nov.) 1937.

2. Rubner, M., and Langstein, L.: Energie und Stoffwechsel zweier frühgeborener Saüglinge, Arch. f. d. ges. Physiol. **39**:39, 1915.

3. Muhl, G.: (*a*) Ueber den Stoffwechsel des gesunden, natürlich ernärhten Sauglings und dessen Beeinflussung durch Fettreduktion der Nahrung, Acta pædiat. **2** (supp.):1, 1923; (*b*) The Fat Absorption and the Calcium Metabolism of Prematurely Born Infants, ibid. **5**:188, 1926.

4. (*a*) Holt, L. E., Jr.; Tidwell, H. C.; Kirk, C. M.; Cross, O. M., and Neale, S.: Studies in Fat Metabolism: I. Fat Absorption in Normal Infants, J. Pediat. **6**:427 (April) 1935. (*b*) Tidwell, H. C.; Holt, L. E., Jr.; Farrow, H. L., and Neale, S.: Studies in Fat Metabolism: II. Fat Absorption in Premature Infants and Twins, ibid. **6**:481 (April) 1935.

5. Ylppö, A.: Das Wachstum der Frühgeborenen von der Geburt bis zum Schulalter, Ztschr. f. Kinderh. **24**:111, 1919.

6. Gordon, H. H.; Levine, S. Z.; Deamer, W. C., and McNamara, H.: Respiratory Metabolism in Infancy and in Childhood: XXIII. Daily Energy Requirements of Premature Infants, Am. J. Dis. Child. **59**:1185 (June) 1940.

half the fat had been removed, such as the one described by Powers,[7] might permit more efficient absorption of food.

In the present paper data from a total of 79 observations on 38 premature and 11 full term infants are reported, and data from observations [8] published previously are included. The results indicate that more than 20 calories per kilogram was lost daily as fecal fat in a third of the observations on premature infants fed diets in which fat supplied from 30 to 55 per cent of the calories (4 to 8 Gm. per kilogram of body weight); the use of half-skimmed milk mixtures, that is, diets in which fat supplied approximately 15 to 20 per cent of the calories (2 Gm. per kilogram), decreased the loss as fecal fat to approximately 10 calories per kilogram, values ordinarily obtained for full term infants with higher intakes of fat.

EXPERIMENTAL PROCEDURE

Subjects.—Feces were collected from 38 healthy premature infants in 67 observations of three to eleven days each for a total of three hundred and fifty-nine days. The recorded birth weights of the infants ranged from 1,060 to 2,300 Gm. and their ages at the beginning of the observations from 6 to 72 days. In 50 observations the infants weighed less than 2,500 Gm. at the beginning, in 11 between 2,500 and 3,000 Gm. and in 6 more than 3,000 Gm. In addition, 11 thriving full term infants were studied in 12 observations totaling sixty-five days. Their recorded birth weights ranged from 2,530 to 4,200 Gm. The results of the observations on the full time infants serve as a standard of comparison for those obtained for the premature infants.

The infants varied in race and sex, and some were products of multiple births. Four premature and 2 full term infants were girls. Eight premature infants and 1 full term infant were Negroes. Five premature infants were twins and 2 were triplets. Although the factors of sex, race and plurality of birth are important in judging the degree of maturity of an infant of any given weight,[9] the small number of infants in each group prevents any definite conclusions from the segregation of results on this basis. The effect of increasing age and weight on fat absorption was judged from repeated observations on individual infants rather than from the results for the whole group.

Diets.—Three types of diet were used in the observations on premature infants. (*a*) Human milk was used in 12 observations on 9 infants. The milk used in all but 1 instance was pooled mother's milk, either fresh or frozen, and it was boiled for five to twenty minutes prior to feeding. (*b*) Cow's milk was

7. Powers, G. F.: Comparison and Interpretation on a Caloric Basis of the Milk Mixtures Used in Infant Feeding, Am. J. Dis. Child. **30**:453 (Oct.) 1925; Infant Feeding: Historical Background and Modern Practice, J. A. M. A. **105**: 753 (Sept. 7) 1935. Dunham, E. C.: The Premature Baby, Washington, D. C., Government Printing Office, 1938.

8. Gordon, Levine, Wheatley and Marples.[1] Gordon, Levine, Deamer and McNamara.[6]

9. Dunham, E. C.; Jenss, R. M., and Christie, A. U.: A Consideration of Race and Sex in Relation to the Growth and Development of Infants, J. Pediat. **14**:156 (Feb.) 1939.

fed in 25 observations on 17 infants. The feeding mixtures consisted of dilutions of evaporated milk in 3 observations, boiled pasteurized whole milk in 1 observation, powdered whole milk in 10 observations and powdered half-skimmed milk, that is, milk from which half the cream had been removed, in 11 observations. Dextrimaltose or cane sugar was used to fortify these mixtures. (*c*) Cow's milk mixtures in which the cream had been replaced by an olive oil preparation (olac) were used in 22 observations on 17 infants. In 8 additional observations on 5 infants a preparation was used which contained only one-half the olive oil customarily present in olac.[10]

In the observations on the 11 full term infants 5 were fed the olive oil preparation and 6 a dilution of powdered whole milk.

Adequate preliminary periods of constant diet of at least two, and usually more, days preceded all periods of collection. The caloric intake and the amounts of protein and fluid ingested were adequate for satisfactory gains in weight. Ten or 20 drops of a concentrate either of vitamin D or of vitamins A and D was administered daily to each infant. Ten, 20 or 25 mg. of ascorbic acid was given daily to 25 of the infants; it was omitted from the diets of 24 infants, in some of whom the intermediary metabolism of the aromatic amino acids[11] was being studied.

For 12 infants the dietary intake was determined by measurement of the food actually retained, according to the method devised by Levine for use in determining water and energy exchange. For the remaining infants the corrected intake was calculated as 95 per cent of the formula as prepared, since 5 per cent was the average amount found in a previous study[6] to be lost by adherence to bottles and nipples and by regurgitation. This method of estimating the intake is unsatisfactory for balance studies, but it introduces no significant error in the present study, in which the chief interest is the fecal fat. Its use permitted study of a larger number of infants, a procedure which was desirable because of the variability observed in the fat excretion of different infants.

All liquid and powdered milks were pooled and analyzed in duplicate or triplicate for fat,[12] nitrogen (Kjeldahl method) and lactose,[13] with the exception of the olive oil preparations, for which the manufacturer's figures for carbohydrate were accepted. For 8 infants given powdered milk preparations chemical analysis of the intake was omitted, and average figures obtained from previous analyses of pooled lots of the same preparation were accepted. The caloric value of the intake was calculated from the content of protein, fat and carbohydrate, with use of the customary constants, 4.1, 9.3 and 4.1 respectively.

Collection and Examination of Feces.—The infants were placed on special mattresses with cutouts for stool containers. The feces were collected separately

10. These preparations were supplied by Mead Johnson & Co.

11. Levine, S. Z.; Marples, E., and Gordon, H. H.: A Defect in the Metabolism of Aromatic Amino Acids in Premature Infants: The Role of Vitamin C, Science **90**:620 (Dec. 29) 1939.

12. Roese-Gottlieb Method, in Official and Tentative Methods of Analysis, Compiled by the Committee on Editing Methods of Analysis, Washington, D. C., Association of Official Agricultural Chemists, 1930, p. 217.

13. Lactose—Official Gravimetric Method of the Association of Agricultural Chemists, in Official and Tentative Methods of Analysis, Compiled by the Committee on Editing Methods of Analysis, Washington, D. C., Association of Official Agricultural Chemists, 1930, p. 216.

from the urine: from boys by using the device of Hoag[14] and from girls by wrapping diapers containing absorbent cotton over the external genitalia. Total fecal fat was determined by the Roese-Gottlieb method[12] in 33 observations on 20 infants; in all other observations the method of Tidwell and Holt[15] was used. The latter method gives information concerning the fat partition as well as the total fat, but in the present paper only the data on total fat are presented.

RESULTS

Fecal Fat Excretion of Full Term Infants.—In table 1 are presented data from 12 observations on 11 infants, ranging in age from 13 to 70 days, who were fed a cow's milk mixture in which milk fat or olive oil supplied from 4.0 to 5.2 Gm. of fat per kilogram (35 to 40 per cent of the total calories fed). In the 6 observations during which the mixture containing milk fat was fed the amount of fecal fat excreted daily varied from 0.6 to 2.0 Gm. per kilogram, and in the 6 observations during which the mixture containing olive oil was used the amount excreted ranged from 0.4 to 0.7 Gm. per kilogram. The fecal fat represented only 10 to 16 per cent of the dietary fat when olive oil was fed and 14 to 41 per cent when milk fat was fed. In 10 of the 12 observations the amount of fecal fat was 1.1 Gm. (10 calories) or less per kilogram.

In 8 observations on 4 infants less than 2¼ months of age who were fed similar amounts of butter fat,[4a] the amount of fecal fat ranged from 0.6 to 1.0 Gm. per kilogram. In one study on a young infant fed olive oil[4a] and in two investigations on infants fed human milk fat[16] the amounts of fecal fat excreted were 0.2, 0.6 and 0.2 Gm. per kilogram, respectively.

These results serve as a standard for comparison with the results of the observations on premature infants.

Fecal Fat Excretion of Prematurely Born Infants Fed Customary Cow's Milk Mixtures.—In table 2 are presented data from 14 observations on 11 infants fed cow's milk mixtures which supplied from 3.7 to 5.8 Gm. of fat per kilogram (from 31 to 46 per cent of the total caloric intake).

By contrast with the full term infants, whose daily excretion of fecal fat was 1.1 Gm. per kilogram or less in all but 2 instances (table 1), the amount of fecal fat excreted by the prematurely born infants on comparable diets ranged from 1.0 to 4.1 Gm. and was 1.9 Gm. or more in 8 of the 14 observations. The proportion of dietary fat excreted in

14. Hoag, L. A.: Apparatus for the Quantitative Collection of Urine and of Stools in Male Infants, Am. J. Dis. Child. **44**:777 (Oct.) 1932.

15. Tidwell, H. C., and Holt, L. E., Jr.: The Estimation of the Total Lipids and the Lipid Partition in Feces, J. Biol. Chem. **112**:605 (Jan.) 1936.

16. Muhl.[3a] Holt, Tidwell, Kirk, Cross and Neale.[4a]

TABLE 1.—*Daily Fecal Fat Excretion of Young, Full Term Infants Fed Cow's Milk Mixtures*

Subject	Observation No.	Duration of Observation, Days	Initial Age, Days	Initial Weight, Gm.	Average Daily Weight Gain, Gm.	Diet		Feces		Fecal Fat					Comment †
						Total Calories per Kg.*	Fat, Gm. per Kg.*	Number of Stools	Dry Weight, Gm. per Kg.*	Percentage of Dry Weight of Stools	Gm. per Kg.*	Percentage of Dietary Fat	Calories per Kg.*	Percentage of Total Dietary Calories	
Milk Fat															
R. F.	F 13	5	13	3,560	66	112	4.7	4	2.7	52	1.4	30	13	12	Cerebral hemorrhage (?)
W. C.‡	F 6	5	26	3,660	24	114	4.3	1	1.2	50	0.6	14	6	5	Cleft palate, harelip
W. B.	F 11	5	33	3,820	52	122	4.9	4	3.0	65	2.0	41	19	16	Cleft palate, harelip
E. H.§	F 14	5	34	3,820	48	124	5.2	3	2.1	49	1.0	19	10	8	Furunculosis
H. G.	F 10	5	39	3,520	20	116	5.0	3	2.4	48	1.1	22	10	9	Hemorrhagic orchitis
K. K.	F 12	4	70	4,080	48	120	5.0	3	2.0	55	1.1	22	10	8	Pyloric stenosis
Olive Oil															
T. T.	F 4	6	26	4,320	37	107	4.0	2	1.1	36	0.4	10	4	4	Cleft palate, harelip
M. O.§	F 9	4	33	4,300	44	119	4.5	3	1.4	34	0.5	11	5	4	Omphalitis
R. C.	F 7	5	37	3,680	56	121	4.6	2	2.1	27	0.6	12	6	5	Cleft palate, harelip
J. R.	F 3	4	39	3,700	35	115	4.3	1	1.7	41	0.7	16	7	6	Bronchopneumonia
J. O.	F 5	12	41	3,520	43	121	4.5	4	1.2	42	0.5	11	5	4	Convulsions
R C.	F 8	5	50	4,300	52	124	4.7	2	1.8	35	0.6	13	6	5	Cleft palate, harelip

* In this and in subsequent tables results are expressed in terms of the average body weight during the observation.
† None of the subjects had symptoms of acute illness at the time of observation.
‡ Negro.
§ Girl.

TABLE 2.—*Daily Fecal Fat Excretion of Prematurely Born Infants Fed Customary Cow's Milk Mixtures*

Subject	Observation No.	Duration of Observation, Days	Initial Age, Days	Initial Weight, Gm.	Average Daily Weight Gain, Gm.	Diet		Feces		Fecal Fat				
						Total Calories per Kg.	Fat, Gm. per Kg.	Number of Stools	Dry Weight, Gm. per Kg.	Percentage of Dry Weight of Stools	Gm. per Kg.	Percentage of Dietary Fat	Calories per Kg.	Percentage of Total Dietary Calories
H. Ab.	107	5	14	1,436	12	110	4.4	6	2.5	56	1.4	32	13	12
I. S.*	110	5	12	1,804	14	118	4.5	6	2.1	57	1.2	27	11	9
L. A.*‡	93	3	25	1,810	30	105	3.9	3	4.4	70	3.1	79	29	28
W. J.†	XVIII	9	19	1,885	20	110	3.7	5	3.1	45	1.4	38	13	12
W. B.	79	6	19	1,920	17	117	4 6	4	2.9	69	2.0	43	19	16
P. S.*	94	4	10	2,008	18	117	4.6	5	3.7	76	2.8	61	26	22
J. S.	104	3	17	2,080	33	125	4.9	3	4.1	76	3.1	61	29	23
F. LaH.	106	3	9	2,192	19	116	4.5	4	2.2	55	1.2	27	11	9
E. Mc.†	4	5	31	2,317	28	118	5.8	5	5.0	74	3.7	64	34	29
I. S.*	112	5	28	2,330	34	112	4.4	4	2.1	48	1.0	21	10	9
T. A.	XVI	5	40	2,640	39	117	5.1	2	2.3	48	1.1	22	10	9
P. A.§	58	7	29	2,740	20	98	4.4	3	2.8	68	1.9	43	17	17
J. S.	113	4	62	3,240	65	140	5.1	3	5.2	79	4.1	80	38	27
J. S.	114	5	72	3,760	40	134	5.0	3	4.1	68	2.8	56	26	19

Fourteen observations, totaling sixty-nine days, were made on 11 subjects.
* Girl.
† Negro.
‡ Twin.
§ Triplet.

the feces ranged from 22 to 80 per cent and exceeded 40 per cent in approximately half the observations. These results confirm the observations of Holt and his co-workers [4b] that premature infants have a defect in ability to absorb butter fat in comparison with full term infants.

No consistent trend was observed in the relation between the fecal fat excretion and the age or the weight of the different infants in this group; the excretion of fecal fat of 2 of the 3 prematurely born infants who weighed more than 2,500 Gm. at the beginning of the observations remained high. Although a birth weight of 2,500 Gm. can be used satisfactorily in statistical studies of large numbers of infants for distinguishing those born prematurely from those born at term, in a small group studied with reference to the single function of fat absorption it obviously does not serve to distinguish the good from the bad absorbers of fat. The results of repeated observations on individual infants studied at different ages will be discussed later.

Fecal Fat Excretion of Prematurely Born Infants Fed Cow's Milk Mixtures in Which Olive Oil Had Been Substituted for Milk Fat.—In table 3 are presented data from 22 observations on 17 infants fed cow's milk mixtures in which olive oil supplied from 3.7 to 5.6 Gm. of fat per kilogram (from 29 to 37 per cent of the total caloric intake). The daily excretion of fecal fat ranged from 0.6 to 3.3 Gm. per kilogram and, in contrast to the consistently low excretion of full term infants (table 1), exceeded 1.1 Gm. in 15 observations and was 1.9 Gm. or more in 11. The proportion of dietary fat excreted in the feces showed a wide range, from 15 to 85 per cent; it was 40 per cent or more in half the observations.

The marked variation in ability to absorb fat of the different infants and of the same infant at different ages (table 5) makes computed averages of doubtful value and vitiates any conclusions drawn from the present data on the relative digestibility of milk fat and olive oil by premature infants. Observations are now being made on the fecal fat excretion with diets containing different types of fats by the same infants in successive periods. For 3 of 4 infants studied in this manner by Holt and his co-workers [4b] the results suggested a greater absorption of olive oil than of milk fat, although, as both his observations and the results of the present study indicate, both types of fat are excreted in greater amounts by premature than by full term infants. The full term infants fed olive oil in the present study consistently excreted less fat than those fed milk fat, but none of these infants was studied in consecutive periods during which both diets were used.

Fecal Fat Excretion of Prematurely Born Infants Fed Human Milk.—In table 4 are presented data from 12 observations on 9 premature infants fed human milk, which supplied from 3.3 to 8.6 Gm. of fat per

TABLE 3.—*Daily Fecal Fat Excretion of Prematurely Born Infants Fed Cow's Milk Mixtures in Which Olive Oil Had Been Substituted for Milk Fat*

Subject	Observation No.	Duration of Observation, Days	Initial Age, Days	Initial Weight, Gm.	Average Daily Weight Gain, Gm.	Diet		Feces		Fecal Fat				
						Total Calories per Kg.	Fat, Gm. per Kg.	Number of Stools	Dry Weight, Gm. per Kg.	Percentage of Dry Weight of Stools	Gm. per Kg.	Percentage of Dietary Fat	Calories per Kg.	Percentage of Total Dietary Calories
H. Ab.	108	4	22	1,570	23	113	4.2	7	2.5	48	1.2	29	11	10
G. C.	38	5	48	1,720	48	122	4.7	4	3.7	70	2.6	55	24	20
R. L.	25	6	47	1,800	48	127	4.8	6	2.0	65	1.3	27	12	9
E. D.*	54	3	31	1,936	35	109	4.2	1	3.2	91	2.9	69	27	25
I. S.†	111	5	20	1,970	46	109	4.1	4	1.9	37	0.7	17	7	6
M. P.	78	7	9	1,980	24	115	4.3	4	2.9	83	2.4	56	22	19
R. E.	33	9	10	2,030	41	116	4.4	3	2.6	77	2.0	45	19	16
J. C.*	97	3	8	2,200	0	112	4.2	5	3.4	68	2.3	55	21	19
D. B.	53	3	16	2,200	10	115	4.4	3	1.7	94	1.6	36	15	13
D. M.	49	4	15	2,226	36	110	4.2	3	2.4	79	1.9	45	18	16
T. R.	89	5	26	2,360	28	108	4.0	1	2.6	73	1.9	48	18	17
R. L.	27	4	60	2,370	35	98	3.7	3	1.2	67	0.8	22	7	7
A. P.	31	9	17	2,375	57	104	4.0	3	1.8	67	1.2	30	11	11
L. O.*‡	5	4	31	2,410	47	125	3.9	8	2.0	55	1.1	28	10	8
E. C.	23	8	20	2,420	35	126	4.8	3	1.6	50	0.8	17	7	6
H. C. A §	65	7	29	2,540	14	105	3.9	4	4.4	75	3.3	85	31	30
H. L.*	18	7	23	2,640	25	132	5.2	3	3.2	66	2.1	40	20	15
R. S.	44	4	32	2,650	46	128	4.9	2	2.8	86	2.4	49	22	17
H. L.*	19	3	35	2,833	31	142	5.6	5	3.4	71	2.4	43	22	15
L. O.*‡	10	4	51	3,220	35	122	3.8	2	1.2	50	0.6	16	6	5
L. O.*‡	12	5	65	3,800	40	126	3.9	4	1.3	46	0.6	15	6	5
J. C.*	99	3	57	3,880	17	119	3.9	2	1.4	50	0.7	18	7	6

Twenty-two observations, totaling one hundred and twelve days, were made on 17 subjects
* Negro.
† Girl.
‡ Twin.
§ Triplet.

TABLE 4.—*Daily Fecal Fat Excretion of Prematurely Born Infants Fed Human Milk*

Subject	Observation No.	Duration of Observation, Days	Initial Age, Days	Initial Weight, Gm.	Average Daily Weight Gain, Gm.	Diet		Feces		Fecal Fat				
						Total Calories per Kg.	Fat, Gm. per Kg.	Number of Stools	Dry Weight, Gm. per Kg.	Percentage of Dry Weight of Stools	Gm. per Kg.	Percentage of Dietary Fat	Calories per Kg.	Percentage of Total Dietary Calories
H. B.*	VII	9	16	1,455	19	121	5.5	4	4.5	67	3.0	58	28	25
R. L.	24	3	41	1,590	20	141	8.2	4	2.9	59	1.7	21	16	11
M. B.	28	9	18	1,720	22	132	6.9	6	4.0	75	3.0	43	28	21
T. A.	XIII	6	19	1,875	38	121	6.0	2	2.3	65	1.5	26	14	12
M. B.	29	11	29	1,920	34	153	8.6	5	3.5	74	2.6	30	24	16
N. O.	1	3	17	1,960	31	123	6.7	3	4.0	55	2.2	33	20	16
V. R.	II	3	21	1,960	23	95	3.3	2	2.8	61	1.7	53	16	17
E. C.	22	3	13	2,080	22	126	7.6	7	2.7	41	1.1	14	10	8
E. Mc.*	3	3	25	2,111	28	103	4.1	2	2.7	63	1.7	41	16	16
G. F.†	XII	3	60	2,338	24	124	5.7	5	3.0	37	1.1	20	10	8
M. B.	30	4	43	2,440	42	145	8.3	5	2.1	71	1.5	18	14	10
V. R.	VI	4	48	2,800	35	106	5.0	3	3.2	16	0.5	10	5	5

Twelve observations, totaling sixty-one days, were made on 9 subjects.
* Negro.

kilogram (from 31 to 56 per cent of the total caloric intake).[17] The amount of fecal fat excreted daily ranged from 0.5 to 3.0 Gm. per kilogram and reached 1.5 Gm. or more in 9 of the 12 observations. Fecal fat represented from 10 to 58 per cent of the dietary fat. These results should not be compared with those for premature infants fed butter fat or olive oil because of the marked variability in fat absorption by individual infants and because of the higher fat content of the diets of human milk. The results do indicate, however, that many premature infants fed human milk excrete an excessive amount of fat.

In all these observations the human milk was boiled prior to feeding, a procedure which Catel has claimed interferes with fat absorption.[18]

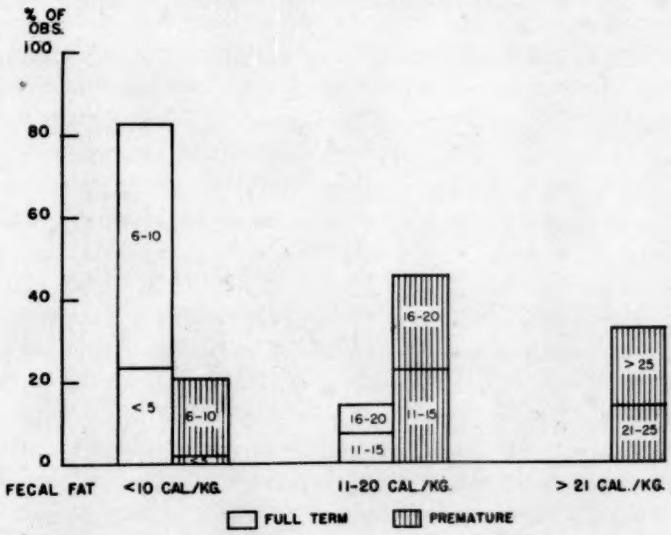

Fig. 1.—Calories per kilogram lost as fecal fat by young infants born at term and born prematurely. The height of each column indicates the percentage of the total number of observations on each group of infants in which the fat excretion reached the level indicated by the figures inside the column.

Rubner and Langstein [2] and Muhl [3] found excessive excretion of fat by 3 of 7 premature infants fed human milk which was presumably unboiled.

Frequency and Magnitude of Deficiency in Ability to Absorb Fat of Infants Fed Customary Diets of Unskimmed Milk.—Figure 1 presents

17. Part of the fluctuation was due to the variability in fat content of different batches of human milk.

18. Catel, W.: Stoffwechseluntersuchungen an Frühgeburten bei Ernährung mit roher und erhitzter Frauenmilch, Deutsche Ztschr. f. Verdauungs- u. Stoffwechselkr. **1**:129, 1938.

Twelve observations, totaling sixty-one days, were made on 9 subjects.

graphically the results of the observations for which data are given in tables 1 to 4 and indicates the frequency and the magnitude of the deficiency in ability of premature infants to absorb fat.

It is seen that whereas in 83 per cent of the observations on full term infants 10 calories per kilogram or less was lost as fecal fat, in only 21 per cent of the observations on infants born prematurely was this low level attained. In 46 per cent of the observations on prematurely born infants the loss was between 11 and 20 calories per kilogram, and in 33 per cent it was above 21 calories per kilogram. The clinical significance of this excessive loss will be discussed later.

Effect of Increasing Age on Fecal Fat Excretion.—In table 5 are presented the results of observations on a group of infants, each of

TABLE 5.—*Effect of Increasing Age on Fecal Fat Excretion of Individual Infants*

Subject	Observation No.	Initial Age, Days	Initial Weight, Kg.	Type of Dietary Fat	Dietary Fat, Gm. per Kg.	Fecal Fat, Calories per Kg.
J. C.	97	8	2.2	Olive oil	4.2	21
	99	57	3.9		3.9	7
M. B.	28	18	1.7	Human milk	6.9	28
	29	29	1.9		8.6	24
	30	43	2.4		8.3	14
V. R.	II	21	2.0	Human milk	3.3	16
	VI	48	2.8		5.0	5
J. S.	104	17	2.1	Cow's milk	4.9	29
	113	62	3.2		5.1	38
	114	72	3.8		5.0	26
H. L.	18	23	2.6	Olive oil	5.2	20
	19	35	2.8		5.6	22
I. S.	110	12	1.8	Cow's milk	4.5	11
	112	28	2.3		4.4	10
L. O.	5	31	2.4	Olive oil	3.9	10
	10	51	3.2		3.8	6
	12	65	3.8		3.9	6
R. L.	25	47	1.8	Olive oil	4.8	12
	27	60	2.4		3.7	7

whom was fed the same type of fat during repeated observations at different ages. The infants are divided into two groups. The first consists of 5 infants who were considered bad fat absorbers; that is, at the time of the initial observations they lost 16 calories per kilogram or more per day as fecal fat. The second is composed of 3 infants who were considered good fat absorbers. For 3 of the 5 infants who absorbed fat poorly (J. C., M. B. and V. R.) the daily caloric loss as fecal fat dropped with increasing age from 21 to 7, from 28 to 14 and from 16 to 5 calories per kilogram, respectively. The fourth infant, J. S., had a defect in fat absorption which was still present at the age of 72 days; at this age this infant lost 26 calories per kilogram per day as fecal fat, as compared with 38 and 29 calories at the ages of 62 and 17 days, respectively. The fifth infant, H. L., showed no significant change in

the excretion of fecal fat in the twelve days that elapsed between the observations. For the 3 infants (I. S., L. O. and R. L.) who had low excretions of fecal fat at the time of the first observations (at the ages of 12, 31 and 47 days respectively) and who were therefore considered good absorbers, the excretion of fecal fat, as would be expected, was low in observations made at later age periods.

The results indicate the marked variability which may exist among infants. For example, I. S. lost only 11 calories per kilogram per day as fecal fat at the age of 12 days, when she weighed 1.8 Kg., while J. S. lost 26 calories at the age of 72 days, when he weighed 3.8 Kg. The variability of the results precludes interpretation in terms of averages and indicates that the defect differs in magnitude from infant to infant and in the same infant at different ages. The data stress one more individualizing factor, namely, the ability to absorb fat, which must be considered in the feeding of premature infants.

Fecal Fat Excretion of Prematurely Born Infants Fed Half-Skimmed Cow's Milk Mixtures.—In table 6 are presented data from 11 observations on 7 infants fed cow's milk mixtures containing only half the fat customarily present and from 8 observations on 5 infants fed a cow's milk mixture containing only half the olive oil customarily present in olac. The intake of fat ranged from 1.7 to 2.3 Gm. per kilogram and supplied from 16 to 20 per cent of the total caloric intake. The excretion of fecal fat ranged only from 0.5 to 1.3 Gm. per kilogram. This range for the premature infants fed half-skimmed milk mixtures corresponds closely to that for young full term infants fed whole milk mixtures (table 1). The proportion of dietary fat lost in the feces ranged from 24 to 72 per cent. Since the amount of fat in the intake differed widely in the observations in which unskimmed and partially skimmed milks were used, no estimates of relative absorption which are based on comparisons of the percentages of dietary fat excreted are justifiable.

Frequency of Stools.—No correlation was found between the frequency of stools and the absolute amount of fat excreted by the infants, none of whom had diarrhea. The number of stools varied from 2 to 7, from 3 to 6 and from 1 to 8 per day for the group of infants fed human milk, cow's milk and the cow's milk-olive oil mixture, respectively, and averaged 4 per day in each group. In the observations on infants fed half-skimmed milk mixtures, the number of stools varied from 2 to 5 and averaged 4 per day. Clinical examinations of the stools were made neither carefully nor consistently. Ylppö [19] noted that premature infants fed human milk or cow's milk had greasy stools much more frequently

19. Ylppö, A.: Zur Physiologie, Klinik und zum Schicksal der Frühgeborenen, Ztschr. f. Kinderh. **24**:1, 1919.

TABLE 6.—*Daily Fecal Fat Excretion of Prematurely Born Infants Fed Diets of Diminished Fat Content (Half-Skimmed Milk)*

Subject	Observation No.	Duration of Observation, Days	Initial Age, Days	Initial Weight, Gm.	Average Daily Weight Gain, Gm.	Diet		Feces		Fecal Fat				
						Total Calories per Kg.	Fat, Gm. per Kg.	Number of Stools	Dry Weight, Gm. per Kg.	Percentage of Dry Weight of Stools	Gm. per Kg.	Percentage of Dietary Fat	Calories per Kg.	Percentage of Total Dietary Calories
Milk Fat														
V. H.*†	83	3	10	1,170	12	114	2.2	3	2.8	46	1.3	59	12	11
L. K.	109	6	27	1,694	28	117	2.3	4	2.3	35	0.8	35	7	6
V. H.*†	84	3	37	1,784	34	105	2.2	2	2.2	41	0.9	41	8	8
A. G.‡	71	7	19	1,800	43	106	2.1	4	2.4	50	1.2	57	11	10
C. S.	85	3	32	1,830	36	112	2.2	3	1.7	41	0.7	32	7	6
P. A§	56	10	6	2,000	31	101	1.7	4	2.1	48	1.0	59	9	9
A. G.‡	72	5	31	2,320	36	106	2.1	5	2.3	43	1.0	48	9	8
P. A.§	57	8	19	2,440	38	102	1.8	5	1.8	44	0.8	44	7	7
V. R.	V	4	40	2,600	20	100	1.9	3	1.6	31	0.5	26	5	5
J. G.	I	5	21	2,720	44	112	2.0	5	2.1	29	0.6	30	6	5
P. A.§	59	9	38	3,020	53	105	2.0	3	1.5	47	0.7	35	7	7
Olive Oil														
H. C. A§	63	11	6	1,800	25	107	2.1	4	2.1	57	1.2	57	11	10
R. Lu.	47	3	14	1,847	38	100	2.2	3	1.8	44	0.8	36	7	7
B. G.‡	75	4	19	2,000	40	106	2.0	2	1.9	68	1.3	65	12	11
R. S.	43	6	14	2,009	46	107	2.3	4	1.9	63	1.2	52	11	10
H. C. A§	64	8	19	2,160	35	104	2.0	3	1.8	61	1.1	55	10	10
B. G.‡	76	8	27	2,300	40	95	1.8	3	1.7	76	1.3	72	12	13
J. C.†	98	5	23	2,600	43	109	2.1	3	1.1	45	0.5	24	5	5
H. C. A§	66	9	38	2,750	42	109	2.0	3	1.4	50	0.7	35	7	6

Nineteen observations, totaling one hundred and seventeen days, were made on 12 subjects.
* Girl.
† Negro.
‡ Twin.
§ Triplet.

than full term infants; accordingly, he fed premature infants partially skimmed breast milk reenforced with sugar and reported good results.

Percentage of Dry Weight of Feces Excreted as Fat.—For the premature infants fed human milk, cow's milk and the cow's milk-olive oil mixture the dry weights of the feces varied from 2.1 to 4.5, from 2.1 to 5.0 and from 1.2 to 4.4 Gm. per kilogram per day, with average values of 3.2, 3.1 and 2.6 Gm., respectively. In the observations on infants fed half-skimmed milk the dry weights of the feces ranged from 1.1 to 2.8 Gm. and averaged 2.0 Gm. per kilogram per day.

In figure 2 the percentage of the dry weight of the feces present as fat is plotted against the total fecal fat excretion in grams per kilogram per day for observations both on premature and on full term infants.

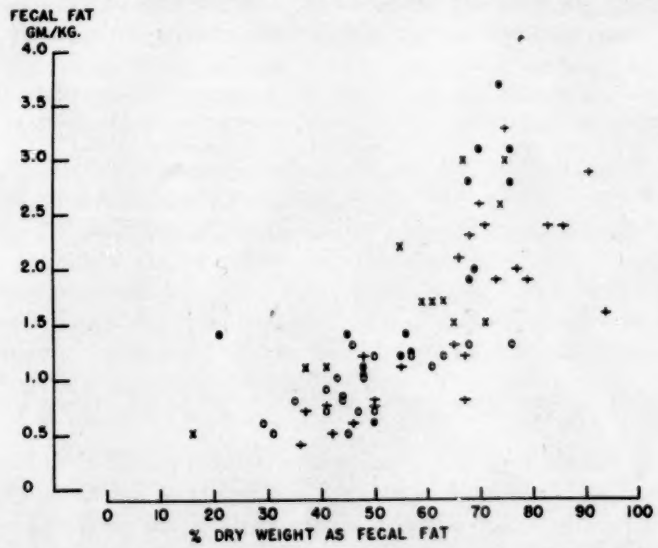

Fig. 2.—Relation of fecal fat to dry weight of stool. The different diets are indicated as follows: x, human milk; the cross, a mixture containing olive oil; the black circle, cow's milk, and the white circle, half-skimmed milk.

As was expected,[4a] the percentage increased as the absolute amount of fat excreted increased, although there was a wide scatter.

In measuring fecal fat excretion the percentage of the dry weight of the feces excreted as fat is sometimes used as a criterion of normal or excessive fat excretion; it eliminates the necessity for accurately timing the periods of collection of feces. The data from the 48 observations on premature infants fed diets of unskimmed milk were arranged to see whether any given percentage could have been used to separate the infants considered good from the infants considered bad fat absorbers. The results are presented in table 7. Sixty per cent was chosen as an

arbitrary dividing line; that is, those premature infants who excreted less than 60 per cent of the dry weight of the stool as fat were considered to have no defect in fat absorption, and those who excreted more than 60 per cent were considered to have such a defect. If an excretion of 1.5 Gm. of fecal fat per kilogram per day is used as the real standard for separating infants with excessive loss of fat from those with normal loss (all but 1 of the full term infants excreted less than 1.5 Gm. [table 1]), it is seen that 16 of the 19 infants who excreted less than 1.5 Gm. of fat per kilogram excreted less than 60 per cent of the dry weight of the feces as fat. Of 29 infants who excreted 1.5 Gm. of fat or more, 27 excreted more than 60 per cent of the dry weight of the feces as fat. In other words, in 43, or approximately 90 per cent of the 48 observations, the arbitrary dividing line of 60 per cent of the dry weight of the feces excreted as fat would have served to separate those

TABLE 7.—*Incidence of Excessive Fecal Fat Excretion in Forty-Eight Observations on Prematurely Born Infants, Determined on the Basis of Percentage of Dry Weight of Feces Excreted as Fat*

Fecal Fat, Gm. per Kg. per Day	Percentage of Dry Weight of Feces Excreted as Fat		
	Less Than 60%	More Than 60%	Total
0.5 to 0.9	6	1	
1.0 to 1.4*	10	2	19
1.5 to 1.9	1	8	
More than 2.0	1	19	29
Total	18	30	48

* All of the full term infants except 1 excreted less than 1.5 Gm. of fat per kilogram per day.

premature infants with an excessive loss of fat from those with normal excretion. As is indicated in figure 2, the scatter of individual observations hampers an exact selection on the basis of the percentage of the dry weight of the feces excreted as fat.

COMMENT

The data demonstrate that many premature infants excrete excessive amounts of fecal fat. Two questions arise: First, what is the cause of this deficiency in ability to absorb fat? Second, is the increased excretion of fecal fat of clinical significance?

The present investigation yields no information as to the cause of the deficiency. Bloor [20] and Frazer [21] have recently summarized the factors involved in the absorption of fat from the intestinal tract.

20. Bloor, W. R.: Fat Transport in the Animal Body, Physiol. Rev. **19**:557 (Oct.) 1939.

21. Frazer, A. C.: Fat Absorption and Its Relationship to Fat Metabolism, Physiol. Rev. **20**:561 (Oct.), 1940.

Pancreatic and enteric lipases and bile salts are important in promoting the splitting of fats and their absorption. Studies of the partition of fecal fat are now in progress which may indicate whether the fault lies in one or both of these mechanisms. Although lipase has been found in the pancreas in human fetuses as early as the fourth, the fifth and the seventh month of fetal life,[22] quantitative measurement of fat-splitting enzymes in the duodenal juices under different dietary conditions might be expected to yield more significant information. The defect may lie in some mechanism other than that of fat splitting or emulsification, however, such as the phosphorylation of fats for transport across the intestinal wall,[23] or it may be related to differences in intestinal motility.[24]

The second question concerns the clinical significance of the increased loss of fat in the stools. The studies herein reported show that full term infants fed approximately 4 to 5 Gm. of fat per kilogram usually lost 10 calories per kilogram or less as fecal fat. Premature infants, on the other hand, fed diets high in fat, such as human milk or a cow's milk mixture containing 4 to 5 Gm. of fat per kilogram, showed this low level of fecal fat excretion in only 21 per cent of the observations; 21 calories per kilogram or more was lost in a third of the observations. In observations during which half-skimmed milk mixtures were fed, however, no infant lost more than 12 calories per kilogram as fecal fat. In other words, the premature infant fed half-skimmed milk behaved consistently, with respect to the excretion of fecal fat, like the full term infant fed an unskimmed milk mixture. That this decreased loss of calories in the stools by infants fed half-skimmed milk mixtures may be of clinical significance is suggested by the results presented in table 8.

Two infants, male members of a set of triplets, were fed virtually isocaloric diets containing from 98 to 105 and from 104 to 109 calories per kilogram in successive periods lasting from seven to eleven days. The total fat intake of each infant was low for the first two periods, during which a half-skimmed milk mixture was fed; then followed a period during which an unskimmed milk mixture was used and an after-period of low fat intake. Adequate preliminary periods of constant diet preceded each collection period. For infant P. A. it is seen that while

22. Needham, J.: Chemical Embryology, London, Cambridge University Press, 1931, vol. 3, table 199, p. 1315.

23. Sinclair, R. G.: The Role of the Phospholipids of the Intestinal Mucosa in Fat Absorption with Additional Data on the Phospholipids of the Liver and Smooth and Skeletal Muscle, J. Biol. Chem. **82**:117 (April) 1929. Sinclair, R. G., and Smith, C.: The Turnover of Phospholipids in the Intestinal Mucosa, ibid. **121**:361 (Oct.) 1937.

24. May, C. D., and McCreary, J. F.: Glucose Tolerance Test in Celiac Disease: Significance of Low Blood Sugar Curves, J. Pediat. **17**:143 (Aug.) 1940.

the half-skimmed milk mixture was being fed the daily caloric loss through fecal fat excretion comprised 9 and 7 per cent of the dietary calories and the daily gain in weight was 14 and 15 Gm. per kilogram. When the unskimmed milk mixture was fed the loss through fecal fat excretion rose to 17 per cent of the dietary calories and the weight gain dropped to 7 Gm. per kilogram. With the resumption of the diet low in fat, the caloric loss dropped to 7 per cent of the intake and the gain in weight rose to 16 Gm. per kilogram. These results were confirmed in the observations on infant H. C. A., for whom the caloric loss through fecal fat excretion represented 6 to 10 per cent of the dietary calories and whose gain in weight was 13 to 15 Gm. per kilogram while the half-skimmed milk was fed. The caloric loss through fecal fat excretion rose to 30 per cent of the dietary calories and the gain in weight dropped to 5 Gm. per kilogram when he was fed the unskimmed milk mixture.

TABLE 8.—*Daily Fecal Fat Excretions and Weight Gains of Two Prematurely Born Infants Fed Equicaloric Diets of Varying Fat Content*

Infant	Observation No.	Duration of Observation, Days	Initial Age, Days	Diet		Fecal Fat		Weight Gain, Gm. per Kg.
				Calories per Kg.	Fat, Gm. per Kg.	Gm. per Kg.	Percentage of Dietary Calories	
P. A.	56	10	6	101	1.7	1.0	9	14
	57	8	19	102	1.8	0.8	7	15
	58	7	29	98	4.4	1.9	17	7
	59	9	38	105	2.0	0.7	7	16
H. C. A.	63	11	6	107	2.1	1.2	10	13
	64	8	19	104	2.0	1.1	10	15
	65	7	29	105	3.9	3.3	30	5
	66	9	38	109	2.0	0.7	6	14

A clinical study is now being made which will permit comparison of the rate of gain in weight of a much larger number of premature infants of the same birth weight, sex and race fed isocaloric mixtures of different fat content under constant conditions of environment and nursing care.

The evidence of defective fat absorption by premature infants fed human milk is not to be construed as controverting the desirability of maintaining the mother's milk secretion until the baby is strong enough to nurse. In the home, the advantages of breast feeding from economic, psychologic and practical standpoints are obvious, both for full term and for premature infants. Intensive efforts [25] should therefore be made to maintain the mother's milk supply in the hope that the infant will be put to the breast after discharge from the nursery.

The feeding of human milk to premature infants under the conditions of nursery practice in large hospitals, however, is as artificial a procedure as the feeding of cow's milk. When human milk is available

25. Koenig, H.: The Care of Premature Infants, Child **5**:65 (Sept.) 1940.

under such conditions, the failure of an infant to gain on an adequate caloric intake is customarily the signal for increasing the intake, and by feeding more of a partially absorbed food one may produce a greater gain in weight. If one accepts the premise that the lowest intake which will insure a satisfactory gain is the safest in the long run,[26] then this can hardly be considered the best practice for premature infants in view of their defective sucking ability, their weak gag and cough reflexes, which permit ready aspiration of food, their weak respirations, which are easily embarrassed by abdominal distention, and the facility with which diarrhea develops in them in the presence of apparently mild infections of the respiratory tract. In a previous study [6] it was established that a total of approximately 120 calories per kilogram (55 calories per pound) covers the total energy requirements of most premature infants over 2 weeks of age. If a premature infant, particularly one who is small or young, fails to gain on such a caloric intake, which in the form of human milk or customary cow's milk mixtures supplies from 35 to 50 per cent of the calories as fat, it would seem more logical to decrease the amount of fat in the mixture by substituting isocaloric amounts of protein or carbohydrate rather than to increase the total caloric intake. In the preparation of cow's milk mixtures this can readily be accomplished by using proper dilutions of powdered or liquid milk preparations from which half the cream has been removed and fortifying them with carbohydrate to achieve the proper total caloric value.[7] In such mixtures protein and fat each form approximately 15 to 20 per cent of the calories and carbohydrate the remaining 60 to 65 per cent. Partial skimming of human milk after centrifugation [27] and addition of sugar [19] or reenforcement with a casein preparation [28] are methods of decreasing the percentage of calories derived from fat while continuing the feeding of human milk. The use of a preparation such as calcium paracaseinate serves to increase both the nitrogen and the calcium intake above the low levels characteristic of unmodified human milk.

Since the absolute amount of fat absorbed by the infants fed the half-skimmed milk mixtures in this study was less than that absorbed from the unskimmed milk diets, one may question whether this limits the value of the former preparation. Clinically, there was no evidence that the infants' needs for essential fatty acids were not met by the

26. Holt, L. E., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, ed. 11, New York, D. Appleton-Century Company, Inc., 1940, p. 133.

27. Salge, B.: Der akute Dünndarmkatarrh des Sauglings, Leipzig, Georg Thieme, 1906; cited by Friedberg, E., and Noeggerath, C.: Enfettete Frauenmilch als Heilnahrung, Arch. f. Kinderh. **68**:195, 1921.

28. Langer, H.: Ueber die Ernährung frühgeborener Kinder in den ersten Lebenswoche, Ztschr. f. Kinderh. **41**:598, 1926.

amount of fat absorbed. The infants gained well and eczema [29] did not develop during their stay in the hospital. The diminished absorption of fat with the feeding of both types of diet, however, is an added reason [30] for giving premature infants large amounts of vitamin A as well as vitamin D, beginning early in life. The higher carbohydrate intake may indicate higher requirements for thiamine.[31]

SUMMARY

The excretion of fecal fat was determined in 79 observations, lasting three to eleven days, on 38 premature and 11 full term infants ranging from 6 to 70 days in age at the beginning of the observations. The full term and premature infants were fed a cow's milk mixture or a cow's milk–olive oil preparation, and some of the premature infants were given human milk. In 19 of the observations on premature infants milk fat or olive oil supplied only half the fat customarily present in the diet.

In 83 per cent of the observations on full term infants the caloric loss through excretion of fecal fat was 10 calories or less per kilogram. In 21 per cent of the observations on premature infants fed unskimmed milk the loss was less than 10 calories per kilogram per day, in 46 per cent it was between 11 and 20 calories and in 33 per cent it was above 21 calories. In all the observations during which partially skimmed milk was fed the caloric loss through the excretion of fecal fat was 12 calories or less per kilogram per day.

A marked variability in the amount of fecal fat excreted was found to exist among different infants and in the same infant at different ages. Three of 5 infants who were poor fat absorbers at the time of the initial observation showed a decreased fecal fat excretion with increasing age. For 2 no improvement was noted during the period of study. No conclusions can be drawn from the present study concerning the relative absorbability of the different fats fed.

The percentage of the dry weight of the feces excreted as fat tended to vary directly with the total amount of fat excreted, although there was a wide scatter. In approximately 90 per cent of the 48 observations on premature infants fed unskimmed milk, the value of 60 per cent of

29. Hansen, A. E.: Study of Iodine Number of Serum Fatty Acids in Infantile Eczema, Proc. Soc. Exper. Biol. & Med. **30**:1198 (May) 1933. Holt and others.[4a]

30. Breese, B. B., Jr., and McCoord, A. B.: Vitamin A Absorption in Celiac Disease, J. Pediat. **15**:183 (Aug.) 1939. May, C. D.; Blackfan, K. D.; McCreary, J. F., and Allen, F. H., Jr.: Clinical Studies of Vitamin A in Infants and in Children, Am. J. Dis. Child. **59**:1167 (June) 1940.

31. Evans, H. M., and Lekovsky, S.: Sparing Action of Fat on the Anti-Neuritic Vitamin, Science **68**:298, 1928. Whipple, D. V., and Church, C. F.: The Composition of Growth Induced by Vitamin B_1, J. Biol. Chem. **114**:cvii, 1936; The Effect of Vitamin B_1 on the Respiratory Quotient, ibid. **119**:ciii, 1937.

the dry weight of the stool excreted as fat served to divide those infants who excreted less than 1.5 Gm. of fat per kilogram per day from those who excreted more than 1.5 Gm.

CONCLUSIONS

A considerable proportion of infants born prematurely were found to excrete an excessive amount of fecal fat when fed customary diets either of boiled human milk or of cow's milk in which fat supplied from 30 to 55 per cent of the calories. The use of half-skimmed milk mixtures, in which fat supplied only 15 to 20 per cent of the calories, was found to be a simple and satisfactory method of decreasing the loss of fat to the level observed for full term infants fed mixtures of unskimmed cow's milk.

DELAYED DEVELOPMENT OF ANTIBODY TO STAPHYLOCOCCUS TOXIN IN DIABETIC CHILDREN

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AND
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The problem of the decreased resistance to infection of the patient with poorly controlled diabetes has been investigated from a variety of viewpoints.[1] Richardson[2] demonstrated that in depancreatized cats there was a lowered nutritional state, accompanied by a decrease in the liver glycogen, which led to low serum agglutination titers after injection of Bacillus typhosus vaccine. The organs of those animals in which there were present several alterations in the body chemistry commonly found in the diabetic patient were definitely more susceptible to dissemination from the focus of infection in the skin than those of normal controls. When the cats were given insulin and were well fed there was no difference between the diabetic and the normal animals in their capacity to produce agglutinins against the typhoid bacillus.

Studies of the production of antistaphylolysin after injection of staphylococcus toxoid were made on a series of diabetic patients by Richeri and Gomez[3] and by Wale and Madders.[4] Unfortunately, their data are meager, and no attempt was made to correlate the state of control of the diabetes with the rate or the intensity of the immune response.

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1. Moen, J. K., and Reimann, H. A.: Immune Reactions in Diabetes, Arch. Int. Med. **51**:789-795 (May) 1933. Marble, A.; White, H. J., and Fernald, A. T.: The Nature of the Lowered Resistance to Infection in Diabetes Mellitus, J. Clin. Investigation **17**:423-430, 1938.

2. Richardson, R.: Immunity in Diabetes: III. Relation of Tissue Glycogen and Blood Chemistry to Bacterial Dissemination, Antibody Formation and Survival After Infection in Diabetes, J. Clin. Investigation **19**:239-250, 1940.

3. Richeri, V. H., and Gomez, O.: Reacción específica de enfermos diabéticos al antígeno. Toxoide estafilocóccico, Semana méd. **2**:127-130, 1938.

4. Wale, R. S., and Madders, K.: Staphylococcal Toxoid in the Treatment of Diabetes, Brit. J. Exper. Path. **17**:279-281, 1936.

METHODS AND MATERIALS

In the present investigation the development of antistaphylolysin (alpha) in the serum of a series of 14 normal children who were housed in an institution was studied, and the titers were compared with those of a similar group of diabetic children who were cared for in the outpatient department of the University of California Hospital. The children were given seven or eight weekly injections of unmodified staphylococcus toxin [5] prepared by the method of Leonard and Holm.[6] Toxin and not toxoid was employed because according to Gernez and Pannéquin [7] it is much the better antigen. The L_h dose was 0.070 cc. and the L_r dose 0.065 cc. The toxin was injected intradermally in a volume of 0.05 cc., beginning with a 1:50 dilution, and the concentration was increased slowly until undiluted toxin was given. The dose was divided and injected into several sites when it became larger than 0.1 cc. The maximum total dose of full strength toxin employed was 0.15 to 0.2 cc., except on one occasion when 0.3 cc. was used. These variations in dosage did not appreciably affect the antibody response.

The injection of the first dose of undiluted toxin usually produced a painful, local inflammation which subsided within forty-eight hours. Subsequent reactions were of diminishing intensity.[8] The course of the diabetes was not influenced by the toxin, and no systemic reactions were observed.

Antibody to staphylococcus toxin was measured by titrating the serum for its content of alpha antistaphylolysin, according to the method of the National Institute of Health.[9] Blood was taken before immunization was begun and approximately every three weeks thereafter.

RESULTS

The data are plotted in figure 1. The ordinates represent the logarithms of the serum titers expressed in international units per cubic centimeter, and the abscissas indicate the number of days after the commencement of immunization. Study of figure 1 reveals individual variations among the normal and the diabetic children in the rate of development of antibody as well as in the maximum titers reached at any time in the course of immunization. The rate of development of alpha antistaphylolysin is much slower in the average diabetic child than in the normal subject (table 1), and the maximum titers attained by the former are somewhat lower than those of the latter (fig. 2).

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5. The preparation used was supplied by E. R. Squibb & Sons.

6. Leonard, G. S., and Holm, A.: A Method for the Production of Staphylococcus Toxin and Toxoid, J. Immunol. **29**:209-223, 1935.

7. Gernez, D., and Pannéquin, C.: L'intradermoréaction à la toxine et à l'anatoxine staphylococciques, Rev. d'immunol. **3**:79-135, 1937.

8. Weiss, C.: A Study of Natural and Acquired Immunity to Staphylococcal Toxin in Monkeys, J. Immunol. **37**:185-200, 1939. Sulzberger, M. B., and Rubin, G.: Staphylococcus Toxin and Staphylococcus Toxoid: A Comparison of the Skin Test Reactions and Evidence of Intracutaneous Immunization as Shown by Skin Tests, ibid. **30**:386-387, 1936.

9. United States Standard Staphylococcus Antitoxin, Memorandum B-1199, National Institute of Health, United States Treasury Department, Public Health Service, January 1936.

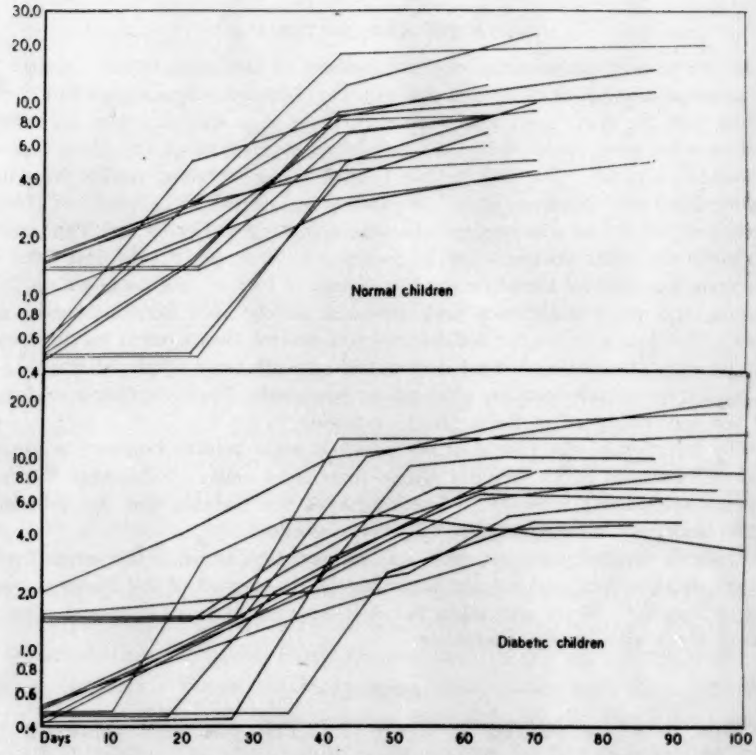

Fig. 1.—Rate of development of antistaphylococcus antibody by a series of 14 normal and 14 diabetic children. The ordinates represent the logarithms of the concentrations of alpha antistaphylolysin in international units per cubic centimeter of serum and the abscissas the number of days after the beginning of immunization.

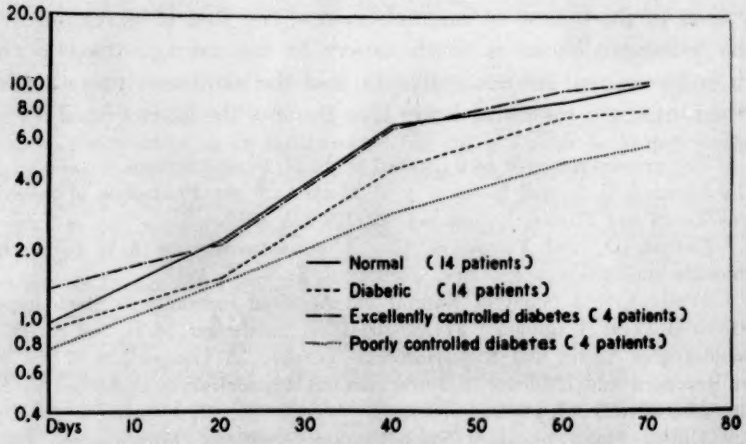

Fig. 2.—Comparison of the antibody production of normal and of diabetic children with special reference to the state of diabetic control.

In order to determine whether or not the rate of development of antibody by the diabetic patient is dependent on the state of control of the disease, the clinical records for each patient, extending over the past one and a half to five years, were examined in order to arrive at a composite picture of the status of diabetic control. The data (table 2), supplied by Dr. Mary B. Olney, include results of blood sugar determinations made before breakfast, during the midmorning, before lunch, in the midafternoon and before supper on test days, which occurred every two to three months. The patients were rated on the basis of the twenty-four hour urinary excretion of sugar, the presence of acetonuria, the blood sugar levels, the occurrence of hypoglycemia during insulin treatment, the frequency of acidosis and of infections and the general state of nutrition. A rank-order correlation, calculated between the order of diabetic control and the order of maximum antilysin response

TABLE 1.—*Serum Titers (Alpha Antistaphylolysin) of Fourteen Normal and Fourteen Diabetic Children at Various Intervals During the Course of Immunization with Staphylococcus Toxin*

Days After Beginning Immunization	Serum Titers *	Number of Children	
		Diabetic	Normal
10	<1	9	4
20	<2	12	7
30	<3	12	5
40	<4	10	4
50	<5	10	4
60	<6	6	4

* Expressed in international units per cubic centimeter of serum.

during immunization, was found to be 0.53 (probable error = 0.136). This value may be interpreted to mean that there are only 4 chances in 1,000 that there is no true relation between the degree of diabetic control and the maximum antilysin response.[10] As shown in figure 2, the 4 diabetic patients whose disease was excellently controlled showed an average curve of serum antibody which, in regard to both the rate of development and the actual titers, is close to that of the normal patients, whereas the 4 patients whose diabetes was in the poorest state of control have an average curve much below that of the normal group.

SUMMARY AND CONCLUSIONS

There was a delay in the development of antibody after intradermal injection of staphylococcus toxin in diabetic children. Not only was there a slower production of alpha antistaphylolysin in their serum, but

10. Dunlap, J. W., and Kurtz, A. K.: Handbook of Statistical Nomographs, Tables, and Formulas, New York, World Book Company, 1932.

TABLE 2.—*Summary of Clinical Data on a Series of Fourteen Diabetic Children*

Patient No.*	Age, Years	Sex	Weight, Kg.	Blood Sugar, Mg. per 100 Cc.	Hypoglycemia	Dextrose in Urine, Gm. per 24 Hr.	Color of Precipitate in Benedict's Test for Glycosuria †	Acetonuria	Severe Acidosis ‡	Infections	Maximum Serum Titer Attained §	Order of Maximum Antistaphylolysin Response
1	10.5	F	28.3	90 to 225	None	4.4	Blue; occasionally green	None	None	Occasional cold	20.0	1.0
2	19	F	53.2	75 to 170; rarely above 200	Frequent (once severe)	4.6	Blue; rarely green or yellow	None	None	Infrequent	4.0	12.5
3	19.5	M	61.6	70 to 200; occasionally above 200	None	4.0	Usually blue	None	Once in 1935	Infrequent	10.0	4.0
4	9.5	M	28.0	80 to 280	None	7.3	Green or red frequently	Occasionally +	None	2 infections of respiratory tract per year	12.5	3.0
5	14	F	55.0	80 to 250; frequently high	None	12.0	Usually green; frequently yellow	None	Mild in 1938	Infrequent	17.0	2.0
6	10	F	37.0	80 to 270, with wide variation	Fairly frequent	8.9	Frequently green	Occasionally +	None	Frequent rhinitis, allergic (?)	7.0	8.5
7	4.75	F	16.0	60 to 354; variable	Occasional (blood sugar 60 mg. per 100 cc.)	5.0	Highly variable	None	None	Frequent infections of upper respiratory tract; otitis media twice; mastoiditis 1940	8.5	5.5
8	9	F	26.5	70 to 250; variable	Frequent	14.0	Frequently orange	Occasionally ++	None	Infrequent	8.5	5.5
9	14.5	M	48.6	90 to 300	Occasional; mild	8.6	Occasionally brick color	Almost always + to ++	Mild in 1935, 1936, 1937, 1937	Chronic sinusitis	3.0	14.0
10	10	F	28.4	55 to 280; variable	Frequent	12.5	Frequently brick color	Frequently +	1932, 1935 (mild), 1938	Frequent, severe infections of upper respiratory tract; pneumonia; mastoiditis; streptococcic infections of throat	7.0	8.5
11	12.5	F	42.5	125 to 300 or 400; usually high	Frequent (blood sugar 50 to 60 mg. per 100 cc.); shock twice in 1938	12.0	Usually brick color, once or twice daily	Frequently ++	1938, 1939 (mild)	2 infections of upper respiratory tract per year	5.0	11.0
12	16.5	F	54.0	120 to 300; usually high	None	22.0	Usually green; frequently yellow	Often ++ or +++	None	2 infections of upper respiratory tract per year	6.0	10.0
13	15	F	54.3	150 to 270; usually high	Occasional	21.0	Frequently brick color	Often ++	1936, 1939	Frequent infections of upper respiratory tract	4.0	12.5
14	13.5	F	41.0	95 to 300; usually high	Rare	29.0	Usually orange, sometimes daily	Frequently ++	None	Frequent infections of upper respiratory tract	8.0	7.0

* The patients are listed in the order of diabetic control, the disease of patients 1 to 4 being in the best and that of patients 11 to 14 in the worst state of control.
† Determined during frequent check-ups over a period of several months or years of observation.
‡ Judged by such indications as the carbon dioxide-combining power of the plasma and symptoms of impending coma.
§ Expressed in international units of alpha antistaphylolysin per cubic centimeter of serum.

the maximum titers attained after several weeks of immunization were lower than those of a similar group of normal children.

A correlation was observed between the state of diabetic control and the antistaphylolysin response of a group of diabetic patients. Diabetic children whose disease was excellently controlled responded in antibody production much like normal children, whereas those whose diabetes was poorly controlled showed a definitely retarded and diminished production of antihemolysin.

Dr. R. Tuddenham, of the Institute of Child Welfare of the University of California, guided us in the statistical interpretation of the data.

Case Reports

RITTER'S DISEASE

REPORT OF A CASE IN WHICH RECOVERY OCCURRED

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AND
DAVID DRAGUTSKY, M.D.
AND
GEORGE ROOK, M.D.
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About sixty-two years ago [1] a rather rare and serious cutaneous disease of early infancy associated with epidermolysis was first described by Ritter von Rittersheim and called dermatitis exfoliativa infantum. Since then various reports have been published, but the nature and the treatment of the disorder have not been definitely determined. In view of this situation, it was thought that a case in which the patient responded well to therapy should be reported, since it might shed further light on the subject of Ritter's disease.

REPORT OF CASE

A. M., a 1 month old white boy was admitted to the hospital on Jan. 15, 1941. Two days prior to admission an eruption had appeared on the thighs and had spread rapidly to the face, the arms and the trunk. The child cried continuously, but his appetite was good and his bowel movements regular.

The infant was delivered normally, his birth weight being 5 pounds 8 ounces (2,495 Gm.). His history was uneventful. Since birth he had been fed a formula of boiled whole milk, but no cod liver oil or orange juice had been given. The mother was a primipara; there was no familial history of syphilis, allergy or other disease.

Examination revealed a malnourished, dehydrated infant, weighing 6 pounds 2 ounces (2,778 Gm.), who was restless and gave a continuous hoarse cry. Both eyelids were edematous and covered with fine scales, and there was a slight discharge at both inner canthi. The throat and the buccal mucous membranes were normal. The heart, the lungs and the abdomen were essentially normal, and no adenopathy was noted.

About the corners of the mouth and the nasolabial folds the skin was fissured and scaly, while scattered over the face were denuded, red, glossy areas. In the

From the Pediatric Service of the Metropolitan Hospital, New York; Dr. Reuel A. Benson, Director.

1. (*a*) Elias, H., and Schachter, M.: Clin. pediat. **16**:47 (Jan.) 1934. (*b*) Barberi, S.: Arch. di ostet. e ginec. **1**:72 (Jan.-Feb.) 1937. (*c*) Ryan, N. W., and Goldman, L.: Treatment of Ritter's Disease with Sulfapyridine: Report of Case with Recovery, Am. J. Dis. Child. **59**:1057 (May) 1940.

axillas and the axillary regions of the chest exfoliation had taken place, leaving shiny red areas surrounded by ragged edges. There were similar areas on the abdomen, interspersed with raised patches which gave the appearance of bullae. The skin of both buttocks was erythematous and wrinkled. The dorsal surfaces

Photograph taken Jan. 17, 1941, showing the marked desquamation of the skin of the face, the neck, the body and the extremities. The darker areas indicate the erythematous regions, as contrasted with the lighter color of the remaining normal skin.

of the hands and fingers were red and desquamated, but no desquamation or scaling was noted on the palms or soles. The Wassermann reaction of the blood was negative.

On the basis of the physical signs and the results of a consultation with the department of dermatology, a diagnosis of Ritter's disease was made.

One-half teaspoon of a syrup containing the vitamin B complex [2] was given three times a day, but the patient's condition became progressively worse. The temperature rose to 102.5 F., six loose stools were passed daily, the infant became toxic and dehydrated and the prognosis appeared grave.

At this time (January 18) was begun the administration of 2 mg. of riboflavin three times a day in addition to the first vitamin preparation, and a mixture of 50 per cent cod liver oil U. S. P. in a base of petrolatum and paraffin was applied to the skin.

The next day the stools began to improve and the child appeared more comfortable and took his feedings well, but the exfoliation had become more extensive. However, from that time on the improvement was so rapid that by January 20 the redness and exfoliation were limited to a few small areas on the trunk. By January 22 no desquamation was present except for a few small regions on the scalp, and the fissures about the lips and alae nasi had disappeared. After this some furuncles developed over the entire fontanel, on the left side of the neck and at the base of one finger nail, but these lesions responded to simple local treatment, and by February 5, the skin was completely clear. The infant was discharged on the following day.

COMMENT

This rare disease occurs in early infancy; usually the onset is between the second and the fifth week after birth.[3] It often affects well developed babies who are breast fed.[4] There is usually no predilection for either sex, although some authors [5] have claimed that it is more common in boys.

The disease passes through two stages [6]; the first is characterized by a generalized inflammation of the skin and the second by suppuration and necrosis.

The disease begins with redness of the skin of the face, especially on the chin and around the corners of the mouth; more rarely the skin

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2. This was given in the form of vitamin B complex syrup, Squibb, which is described in the manufacturer's catalogue as follows:

"A highly concentrated preparation of the whole natural vitamin B complex as derived from rice bran, fortified with crystalline thiamine hydrochloride and riboflavin. One teaspoonful (5 cc.) has the vitamin activity of: 250 U. S. P. XI units thiamine; 750 micrograms riboflavin; 500 micrograms (approx.) pyridoxine; 1875 micrograms (approx.) panthothenic acid."

3. (*a*) Raschkes, I.: Arch. f. Gynäk. **139**:669, 1930. (*b*) Finnerud, C. W., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 4, chap. 40, p. 18.

4. (*a*) Wieland, E.: Schweiz. med. Wchnschr. **52**:1165 (Dec. 21) 1922. (*b*) Elias and Schachter.[1a] (*c*) Barberi.[1b]

5. Elias and Schachter.[1a] Finnerud.[3b]

6. Flusser, E.: Monatschr. f. Kinderh. **67**:279, 1936.

of the neck, the chest and the back is involved.[7] The erythema spreads quickly, so that the rest of the face, the body and the extremities are covered in two or three days, and fissures [8] may be noted at the commissures of the lips. Then in the involved areas vesicles or bullae,[9] filled with turbid fluid, may appear. However, these are not common [3b] and at times are so transitory [1a] that they are not noticed. The bullae rupture easily,[1b] leaving an inflamed area. The skin shows a tendency to rapid exfoliation, leaving reddish areas which cause the infant to appear as if he had been scalded. A characteristic feature of this phase is epidermolysis [1]; that is, if pressure is exerted on a region of apparently normal skin, the epidermis becomes detached from the underlying tissue (Nikolsky's sign).

In most cases [10] the course of the disease is rapid, and there is almost total exfoliation in one to three days.

Secondary infections,[11] such as pyoderma, furunculosis, sepsis, gangrene, bronchopneumonia and disturbances of the gastrointestinal tract, are frequent.

The more extensive the dermatitis, the more rapid the progress of the exfoliation, the greater the number of bullae, the higher the temperature and the more severe the constitutional symptoms, the worse is the prognosis.[12] In cases of the severe form of the disease death [1b] usually results by the end of the first week. In cases of the mild form of the disease there is no fever, all of the cutaneous manifestations are milder and progress more slowly, the general condition is not affected and signs of improvement are noted in four to five days.[13]

The cause of Ritter's disease is still obscure,[14] although many authors [15] have classified the disorder as a pyogenic infection due to the staphylococcus, while others [16] have expressed the belief that it may be

7. (*a*) Daveo and Bassargette: Bull. Soc. d'obst. et de gynéc. **24**:150 (Feb.) 1935. (*b*) Kendall, N., and Aegerter, E. E.: J. Pediat. **15**:733 (Nov.) 1939. (*c*) Elias and Schackter.[1a] (*d*) Barberi.[1b] Finnerud.[3b]

8. Barberi.[1b] Finnerud.[3b]

9. Barberi.[1b] Daveo and Bassargette.[7a]

10. Footnote 1. Kendall and Aegerter.[7b]

11. Barberi.[1b] Footnote 3.

12. Elias and Schachter.[1a] Barberi.[1b] Raschkes.[3a]

13. Barberi.[1b] Raschkes.[3a]

14. Hallez, G. L.: Nourrison **20**:270 (Sept.) 1932. Kendall and Aegerter.[7b]

15. Elias and Schackter.[1a] Ryan and Goldman.[1c] Wieland.[4a] Flusser.[6] Daveo and Bassargette.[7a]

16. Adamson, H. G.; Thursfield, H., and Paterson, D.: Diseases of Children, Baltimore, William Wood & Company, 1934, p. 1109. Holt, L. E., Jr., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, ed. 10, New York, D. Appleton and Company, 1933, p. 709. Raschkes.[3a] Wieland.[4a]

a form of pemphigus. Some writers [17] have expressed the opinion that the newborn child in whom the disease develops has an especially vulnerable skin or that a congenital weakness of the cutaneous system due to pathologic processes operative during pregnancy may be present.[4g]

However, the results obtained in the present case led to the point of view that the condition may be primarily an avitaminosis, due mainly to a deficiency of the riboflavin portion of the vitamin B complex, associated with a secondary staphylococcic infection. This viewpoint is somewhat substantiated by the fact that in one study [18] of patients with riboflavin deficiency ocular manifestations and lesions around the mouth resembling those observed in this case were noted and, though 80 per cent of the smears and cultures showed Staphylococcus aureus and 20 per cent showed Streptococcus haemolyticus, the administration of riboflavin alone cleared up all of the lesions. Moreover, in other reports on cases of riboflavin deficiency [19] lesions about the mouth and in the nasolabial region similar to those which occurred in the present case have been described.

Although pathologic studies have yielded no specific data [20] which could be used in the classification of the disease, some investigators [21] have observed marked atrophy of the epidermis, with parakeratotic patches and disappearance of the stratum granulosum and stratum lucidum, while in 1 case [22] all of the organs showed stenosing arteritis.

In the past the mortality rate has ranged from 50 to 76 per cent.[23] Treatment has usually consisted of the institution of hygienic measures, the avoidance of unnecessary handling and breast feeding. Recently, some successful results have been reported with the use of an antiseptic, rivanol (2,ethoxyl-6,9-diaminoacridinium hydrochloride),[21] in 2 cases, sulfapyridine (2-[paraaminobenzenesulfonamido] pyridine) in 1 [1c] and sulfathiazole (2-[paraaminobenzenesulfonamido] thiazole) in 1.[24] Some workers have obtained good results from the injection of human serum (10 to 20 cc.) or maternal blood daily, while others have advocated exposures to ultraviolet light for thirty to seventy seconds.

In the present case, from the time that riboflavin was given in the larger dosage there was rapid and remarkable improvement. This

17. Barberi.[1b] Wieland.[4a]

18. Spies, T. D.; Bena, W. B.; Vilter, R. W., and Huff, N. E.: Am. J. M. Sc. **200**:697 (Nov.) 1940.

19. Murphy, R. G., and Damarjian, E.: Rhode Island M. J. **23**:114 (July) 1940. Shields, W. P.: New England J. Med. **223**:215 (Aug. 8) 1940.

20. Volckers, H.: Med. Klin. **12**:1337 (Aug. 27) 1926.

21. Elias and Schachter.[1a] Barberi.[1b]

22. Cailliau, F., and Fleury, J.: Ann. d'anat. path. **11**:911 (Dec.) 1936.

23. Barberi.[1b] Ryan and Goldman.[1c] Raschkes.[3a] Finnerud.[3b]

24. De Sanctis, A. G., and De Lorenzo, F. C.: New York State J. Med. **41**: 1361 (July 1) 1941.

therapeutic result gives rise to the belief that this vitamin may be the key necessary to unlock the puzzle of Ritter's disease.

SUMMARY AND CONCLUSIONS

A case of Ritter's disease is reported in which vitamin therapy, preeminently the administration of riboflavin, gave an astonishingly rapid and successful result.

The assumption derived from this remarkable result was that the disease may be due to a primary vitamin deficiency on which is superimposed a secondary bacterial infection of the devitaminized tissues.

Further observation is essential to establish the validity of this point of view.

REPEATED ATTACKS OF MEASLES

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BROOKLYN

The possibility of a second attack of measles is a subject which has intrigued medical observers for years. Some clinicians admit the possibility, albeit grudgingly, while others, equally competent, believe that such attacks do occur. A second attack must be distinguished from a relapse, which is in reality a second attack that occurs while the patient is still under treatment for the primary attack. Rolleston and Ronaldson [1] noted only 9 cases of relapse in 11,749 cases of measles and claimed that in several cases of so-called relapse the prodromal rash has been mistaken for the primary attack.

Salzmann [2] reported from the literature 36 cases of repeated attacks of measles, in which the patient was seen by the same observer during each attack; there were 21 examples of a third attack and 2 of a fourth attack. She commented on the frequency with which repeated attacks occurred in the same family, thus hinting at a familial deficiency of immunity. The cases reviewed showed nothing characteristic in the prodromes, the symptoms and the course of the second attack. As a rule, when a second attack of measles does occur it is rarely as severe as the first. Macciotta [3] studied 8 cases of relapse and 3 cases of a second attack. In his series, tuberculosis seemed to lower the resistance of the patient to subsequent attacks. Vergely [4] studied the case of a boy who had two definite attacks of measles in two years. Combay [5] flatly denied that a second attack can occur and called all occurrences so labeled errors of diagnosis. The Thomsons,[6] in their excellent monograph, attempted to explain the occurrence of a second attack on the basis of an inadequate

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From the Medical Service of the Jewish Hospital of Brooklyn and the Surgical Service of the Beth Moses Hospital.

1. Rolleston, J. D., and Ronaldson, G. W.: Acute Infectious Diseases, St. Louis, C. V. Mosby Company, 1940, p. 278.

2. Salzmann, M.: Repeated Attacks of Measles, M. Sc. Abstr. & Rev. **5**:486, 1922.

3. Macciotta, G.: Relapses and Second Attacks of Measles, Policlinico (sez. prat.) **32**:116 (Jan. 26) 1925.

4. Vergely, J.: Second Attacks of Measles, J. de méd. de Bordeaux **55**:370 (May 10) 1925.

5. Combay, J.: Preventive Treatment of Measles, Arch. de méd. d. enf. **25**: 614, 1922.

6. Thomson, D., and Thomson, R.: Rôle of Streptococci in Measles, Pickett-Thomson Research Lab. **7**:258 (July) 1931.

development of immunity for some reason during the first attack. Erdheim [7] reported the cases of 2 brothers who had second attacks. A familial predisposition had been noted previously by many observers. Stenn and Stenn [8] have covered the late literature on this interesting condition and have themselves reported a case of relapse.

The cases of measles about to be presented are interesting because of the following points: The first case, I believe, is an undoubted instance of a second attack of measles. In the prodromal stage there was an attack of severe abdominal pain and tenderness, especially in the right lower quadrant, which was suspected of indicating an acute surgical condition. There was also a delay in the appearance of the rash. The second case is that of a second attack in a child who was personally observed during both attacks.

REPORT OF CASES

CASE 1.—R. F., an 8 year old boy of normal height and weight, was well until the onset of the present illness. At 26 weeks of age the child had had measles, with typical oculonasal catarrah, Koplik spots, fever and a rash of five days' duration, which cleared up without complication. During the present illness there was an elevation of temperature in the evening to 101 F. for a period of thirteen days. There were no other symptoms except a hacking cough. On the eleventh day of febrile oscillation, there developed marked abdominal pain, especially in the lower portion of the abdomen. Tenderness was most marked in the right lower quadrant of the abdomen. There was no spasm or rigidity. The blood count revealed 8,000 white cells per cubic millimeter, with 60 per cent polymorphonuclear leukocytes. An ice bag was applied to the right lower quadrant of the abdomen. That evening the abdominal pain and tenderness were less. Examination of the mouth at this time revealed one Koplik spot on the mucosal surface of the right cheek. A light pink, elevated, irregular eruption became visible. Measles was thought of, but that diagnosis could not be reconciled with the previous history. That evening there developed a profuse oculonasal discharge and later a typical measles rash, consisting of crescentic, confluent groups of erythematous maculopapular lesions. The temperature rose to 104 F. The rash lasted five days, and the patient recovered without further incident.

Contact was made with the physician who saw the patient during the first attack. His statement [9] follows: "I have seen only 2 cases in which typical measles occurred in children under 1 year of age, and this child was one of the 2 patients. His case stands out clearly in my mind because of his age. There were typical Koplik spots, conjunctivitis, nasal discharge and a rash accompanied by a high temperature. The case was definitely not an instance of roseola infantum."

During the second attack this patient also had a less frequent symptom of measles, general and local abdominal pain, which confused the attendant. This pain was undoubtedly due to Koplik spots in the cecum and other parts of the

7. Erdheim, S.: Second Attacks in Measles, Brit. J. Child. Dis. **23**:195 (July-Sept.) 1926.

8. Stenn, F., and Stenn, H.: Recidivating Measles, Am. J. Dis. Child. **57**: 368 (Feb.) 1939.

9. Personal communication to the author.

colon. Hobson[10] demonstrated Koplik spots in the colon of a patient with measles who had a colostomy. However, all abdominal pain in cases of measles is not due to Koplik spots in the colon. I have personal knowledge of several instances of gangrenous appendicitis complicating measles, and several cases in which this complication occurred have been reported in the literature.[11] Consequently, one should weigh the facts in each case carefully. In this case the severe abdominal pain preceded the rash and declined after the rash appeared.

CASE 2.—C. V., a 9 year old girl, had a history of mild, typical, uncomplicated measles, preceded by oculonasal discharge and typical Koplik spots, which occurred one year before the second attack, which is to be described. In addition, at the age of 1 year, German measles appeared several days after a vaccination which did not take; this apparently was a coincidence. Three years ago the child had rheumatic fever with carditis, resulting in mitral insufficiency with murmur. Two weeks after an exposure to measles in a younger sister, typical symptoms of this disease developed in C. V., namely, conjunctivitis, running of the nose, several Koplik spots on the inside of the cheek and the characteristic measles rash. The temperature rose to 103 F. and continued at that level for several days. The recovery was without incident.

COMMENT

The Thomsons,[6] who have adequately reviewed many of the aspects of the subject of second attacks of measles, have expressed the belief that such attacks occur in epidemics and in those persons who have had a mild attack of measles in childhood or whose first attack was prolonged and complicated in some way so that adequate immunity did not develop. The patient in case 1 had his first attack at approximately 6 months of age. This is a period of relative immunity to measles. An attack during this time, especially if mild, would not cause the development of a sufficient number of antibodies to protect the host, because his reactivity to the measles virus at this point would not be great. For the same reason, most authorities do not advise immunization against diphtheria during the first six months of life, which is a period of relative immunity to diphtheria also. The second attack of measles in this patient was unusual also because of the delay in the appearance of the rash.[12] There was apparently a slight immunity from the first attack of measles, but it was not sufficient to prevent the second attack.

The second case is that of a child with rheumatic fever who had a mild attack of measles in a nonepidemic year and a second attack during

10. Hobson, F. C.: Koplik Spots in the Colon, Lancet **2**:134 (Aug. 3) 1940.

11. Hudson, H. W., Jr., and Krakower, C.: Acute Appendicitis and Measles, New England J. Med. **215**:59 (July 9) 1936. Polony, S.: Case of Painful Abdominal Syndrome Due to Rash Preceding Measles, Mém. Acad. de chir. **63**: 1038 (Oct. 20) 1937. Gonzalez, H. D., and Dalto, H.: Appendicitis and Peritonitis Due to Measles, Prensa méd. argent. **26**:412 (Feb. 22) 1939. Angel, E., and Kizinski, A.: Acute Appendicitis in Measles, South. Med. & Surg. **100**:222 (May) 1938.

12. Selby, R.: Delayed Rash in Measles, Brit. M. J. **1**:262 (Feb. 8) 1936.

a severe epidemic. That the infection with the rheumatic fever virus had something to do with the lack of development of immunity to the measles virus is but a speculation.

The patients in both of these cases were studied in the epidemic year 1940-1941.

SUMMARY

Two cases of a second attack of measles are presented. In the first case the following points are demonstrated: (1) possible lack of development of immunity to measles in a child who had an attack during a relatively immune period of life, (2) delay in the appearance of the measles rash and (3) abdominal pain of some severity which began before the onset of the rash and disappeared after the rash developed. In the second case a second attack of measles occurred after a mild first attack in a nonepidemic year.

RENAL THROMBOSIS WITH INFARCTION COMPLICATING DIARRHEA OF THE NEWBORN

SUMMARY OF FIVE CASES

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A review of the literature of the last three decades reveals a paucity of reports of hemorrhagic infarction of the kidney associated with thrombosis of the renal vein occurring as a complication of diarrhea of the newborn. Considering the frequent outbreaks of infectious diarrhea in epidemic form in various hospital nurseries, it is surprising that more complications of this nature have not occurred at some time during the course of such an epidemic. We realize that the presence of such complications is masked, clinically, by the gastroenteritis and that they are not apt to be diagnosed during life. However, the outcome is often fatal, and ample opportunity is therefore afforded for postmortem studies. There was only 1 instance of renal infarction in all the reported cases of epidemic diarrhea of the newborn in which necropsy was performed. This was included in the series reported by Jampolis and his co-workers.[1] The only evidence of renal involvement found by Abramson and Frant,[2] in a study of a large series of cases of diarrhea of the newborn, was cloudy swelling of the kidneys.

In the observations recorded in the older European literature there is a plethora of information on this subject. The first full description of the condition was recorded by Rayer [3] in 1837. Von Beckman [4] in 1858

From the Departments of Pediatrics and Pathology of the Morrisania City Hospital.

1. Jampolis, M.; Howell, K. M.; Calvin, J. K., and Leventhal, M. L.: Bacillus Mucosus Infection of the Newborn, Am. J. Dis. Child. **43**:70 (Jan.) 1932.

2. Abramson, H., and Frant, S.: Epidemic Diarrhea of the Newborn, Am. J. Dis. Child. **55**:1288 (June) 1938.

3. Rayer, P. F. O.: Traité des maladies des reins, Paris, J. B. Baillière, 1837-1841; cited by Hutinel.[6]

4. von Beckman, O.: Ueber Thrombose der Nierenvene bei Kindern, Verhandl. d. phys. med. Gesellsch. in Würzburg **9**:201, 1858.

reported 10 cases encountered in a period of nine months. Pollak [5] observed 12 cases in 1871. In a monograph on circulatory disturbance in the newborn, published in 1877, Hutinel [6] included 42 cases of renal thrombosis. He found this condition present bilaterally in 30 cases and pointed out the predisposition of the newborn infant to venous thrombosis in general and to renal thrombosis in particular. Since then only a few isolated reports have appeared in the literature. The most recent cases recorded have been those of Nordwall,[7] Marshall and Whapham [8] and Behr.[9]

In the last few years several epidemics of diarrhea of the newborn, varying in severity, have occurred at the Morrisania City Hospital. The first two outbreaks, reported on by Barenberg, Levy and Grand,[10] were characterized by a high morbidity and mortality. The diarrhea was complicated by superimposed infections, such as bronchopneumonia and otitis media. The complications were responsible for the fatal termination of many of the cases. The clinical course and the physical findings in the whole group of cases of fatal termination did not differ in any respect from those in which renal infarction and thrombosis were present. An opportunity was afforded to perform a necropsy in 25 cases. In addition to other pathologic changes in various organs, in 2 cases there was unilateral thrombosis of the renal vein with infarction and in 2 unilateral infarction without thrombosis. In the fifth case there were infarcts in both kidneys without thrombosis of the renal veins.

The fact that the 5 cases for which data are to be reported in this paper represent 20 per cent of the cases in which autopsy was performed brings out more forcibly the point that this condition is by no means as rare as the lack of reports leads one to believe. Our experience with renal involvement occurring in cases of diarrhea of the newborn was therefore deemed worthy of reporting.

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5. Pollak, O.: Ueber Nierenblutung im Säuglingsalter eine Nachkrankheit des Darmkatarrhes, Wien. med. Presse **12**:457, 1871.

6. Hutinel, V.: Contribution à l'étude des troubles de la circulation veineuse chez l'enfant et en particulier chez le nouveau-né, Thesis, Paris, no. 230, Paris, Delahaye, 1877.

7. Nordwall, W.: Un cas de thrombose bilatérale de la veine rénale chez un nouveau-né, Acta pædiat. **14**:186, 1932.

8. Marshall, S., and Whapham, E.: Case of Bilateral Renal Infarction in a Newly Born Infant, Lancet **2**:428, 1936.

9. Behr, E.: Les altérations morphologiques du rein dans la thrombose de la veine rénale, Arch. internat. de méd. expér. **13**:273, 1938.

10. Barenberg, L. H.; Levy, W., and Grand, M. J. H.: An Epidemic of Infectious Diarrhea in the Newborn, J. A. M. A. **106**:1256 (April 11) 1936.

Data in Five Cases of Renal Thrombosis with Infarction Complicating Epidemic Diarrhea of the Newborn

	Clinical Data				
Case No.	1	2	3	4	5
Birth weight, Gm....	3,632	3,004	4,142	2,724	3,660
Weight at onset of diarrhea, Gm.	3,262	2,270	3,972	2,752	3,604
Age at onset of diarrhea, days	3	8	3	12	13
Age at death, days...	14	12	7	20	20
Stools:					
Character at onset	Watery, with mucus and few streaks of blood	Loose, yellow	Loose, yellow	Loose, green, with mucus	Watery, yellow
Average number per day	4-5	5-6	8-11	5-12	4-5
Reaction	Acid	Acid	Acid	Acid	Acid
Vomiting, day of onset	None	9th	4th	15th	13th
Physical Examination:					
On admission	Negative	Dehydration	Negative	Throat red	Dehydration and rales at bases of lungs
Later	Dehydration	Sore buttocks	Dehydration, toxic	Toxemia	Toxemia
Duration of complications, days:					
Pharyngitis	4	9	..	12	16
Otitis media	6	9	..	12	..
Thrush	11	8	..	14	18
Bronchopneumonia	..	12	6	..	18
Purulent conjunctivitis	13	..	..	..	..
Urine:					
Day examined	4th 9th	11th 5th	5th	16th	19th
Sugar	— —	— —	—	—	3+
Albumin	Trace Trace	— —	—	—	Trace
Red blood cells.....	— —	— —	—	Occasional	Occasional
White blood cells...	Occasional Occasional	Occasional Occasional	Occasional	Occasional	Occasional
Blood culture	.....	Sterile, 10th day	Sterile, 4th and 6th days	Sterile, 17th day	Sterile, 17th day

	Postmortem Examinations									
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
Kidneys, gross:										
Size	1½ times normal	Normal	1½ times normal	Normal	Normal	Normal	1½ times normal	Slightly enlarged	Normal	2 times normal
Consistency	Soft	Normal	Soft	Normal	Soft	Soft	Soft	Soft	Normal	Soft
Color	Deep red	Normal	Cyanotic	Red	Deep red	Deep red	Deep red	Red	Normal	Purple
Color on section	Purple	Red	Purple	Red	Deep red	Deep red	Purple	Red	Normal	Purple
Renal markings	Absent	Normal	Indistinct	Normal	Normal	Normal	Normal	Normal	Normal	Absent
Thrombus in main vein *	2.5 cm.	—	—	—	—	—	1.5 cm.	—	—	—
Microscopic: †										
Hemorrhage in interstitial tissues	Marked	Slight	Marked	—	Moderate	Moderate	Marked	Moderate	—	Marked
Hemorrhage in tubules	Marked	—	Marked	—	Moderate	Moderate	Marked	Moderate	—	Marked
Glomeruli	Necrotic	Normal	Necrotic	Normal	Normal	Normal	Necrotic	Normal	Normal	Necrotic
Tubules	Necrotic	Cloudy swelling	Necrotic	Normal	Partially necrotic	Partially necrotic	Necrotic	Degenerated	Normal	Necrotic
Engorgement of blood vessels	Marked	Moderate	Marked	Moderate	Moderate	Moderate	Marked	Moderate	Moderate	Marked
Thrombi	—	—	Present	—	Occasional	Occasional	Numerous	—	—	Numerous
Other organs:										
Thrombi	–		—		—		—		—	
Bronchopneumonia	–		Lower lobe		Lower lobe		–		Lower lobe	

In all cases except case 5, in which there was mild toxemia, the antepartum course and delivery were uneventful and the maternal Wassermann reaction was negative.

* There were no thrombi in the branches of the renal veins.

† No bacteria were observed in the microscopic sections. In all cases the walls of the renal veins were normal.

DATA IN FIVE CASES OF RENAL THROMBOSIS WITH INFARCTION COMPLICATING EPIDEMIC DIARRHEA OF THE NEWBORN

In cases of thrombosis of the cerebral and dural sinuses the symptoms and signs become apparent as soon as an intracranial injury is produced by a thrombus, and a diagnosis may, therefore, be made during the course of the illness. The difficulty in making a diagnosis in cases of thrombosis of a renal vein is caused by the absence or vagueness of the urinary abnormalities. A glance at the table, which contains data for the 5 cases in which such thrombosis occurred, reveals that a correct diagnosis could not be made from the clinical and laboratory data. Hemoglobinuria, anuria and icteric tinge to the skin, which are often present in the cases of older patients with renal thrombosis, were absent in our cases. The urinary abnormalities consisted mainly of a trace of albumin and occasional white and red blood cells. In this respect, the results of urinalyses in these cases did not differ from those in the cases in which renal involvement was not observed at necropsy. For that matter, in the cases of the infants who eventually recovered from the diarrhea the urinary findings were similar. Whether the short duration and the fatal course of the disease in the cases presented were responsible for the absence of urinary symptoms we are unable to state. In this connection it is important to bear in mind the possibility that the infants who recovered from the diarrhea had renal thrombosis but the circulation of the kidney was partially or completely restored, depending, of course, on the degree of renal involvement, in the course of time. It is conceivable that such kidneys are more susceptible to infections during infancy and childhood and may account for some of the cases of obscure nephritis.

From our data we are able to rule out the possibility that such conditions as syphilis, toxemia during pregnancy, trauma by pressure exerted on the kidney regions during delivery or prematurity acted as contributing factors. The Wassermann reactions of the mothers during pregnancy were negative. The antepartum course of the mothers was entirely normal except in case 5, in which a history of mild toxemia early in pregnancy was obtained. None of the infants was premature or immature. They were all normal, well developed and without congenital defects. The birth weights of 3 were above the average, ranging from 3,632 to 4,142 Gm.; the smallest weighed 2,724 Gm.

It has been generally accepted that young infants, especially during the neonatal period, are resistant to the usual infections of the upper respiratory tract. Apparently the epidemic diarrhea had lowered the resistance of our patients to such infections. During the course of illness such complications as sore throat, otitis media and bronchopneumonia developed. The possibility that renal infarction and

thrombosis resulted from a combination of diarrhea and a superimposed infection will be discussed subsequently.

Gross Pathologic Changes in Kidneys.—The affected kidney was markedly enlarged in the 4 cases (1, 2, 4 and 5) in which unilateral total infarction took place, being from one and a half to two times the size of the normal kidney. In case 3, however, in which bilateral partial infarction occurred, the kidneys were of practically normal size. The

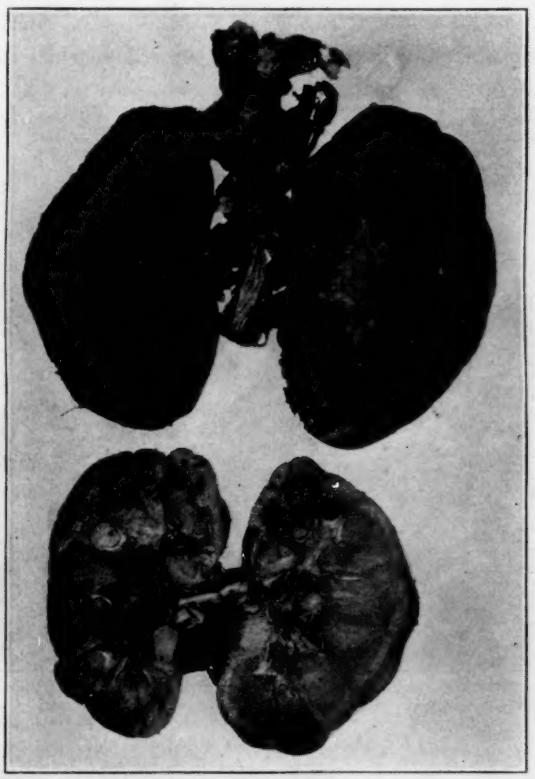

Fig. 1.—The right kidney (upper) is larger than the left (lower) and is markedly congested. Note the presence of a thrombus in the right main renal vein in the cut section.

color of the kidneys varied from deep red to dark purple, and they were soft. On opening the capsule, which stripped with ease, the organ bulged out. In 1 case a thin film of blood covered the smooth surface of the kidney. On section little renal structure could be seen, the whole organ being diffusely infiltrated with blood; there was complete absence of demarcation between the cortex and the medulla. In 2 cases, only at the very rim of the kidney was any tissue left that could be identified

as renal cortex, the presence of which indicated, as Fahr [11] pointed out, the existence of a normal circulation because of the anastomosis of the renal vessels with those of the renal capsule. In 2 cases (1 and 4) a nonadherent thrombus, measuring 2.5 cm. in one instance and 1.5 cm. in the other, was lodged in the main renal vein (fig. 1 and 2). There was no extension of the thrombus from the main vein into the branches. This coincides with the experience of Hutinel,[6] who stated that the thrombus in most of his cases occupied the main trunk of the renal vein.

Microscopic Pathologic Changes in Kidneys.—In general, the microscopic sections of the affected kidneys showed marked destruction of

Fig. 2.—Right kidney, showing marked engorgement and the thrombus in the main renal vein.

the glomeruli and the tubules; only an occasional glomerulus retained its structure. A feature common to these organs was diapedesis of the red blood cells, amounting practically to hemorrhage, in the interstitial tissues. The same was true of the veins and capillaries; these structures in all the affected kidneys were markedly engorged with blood elements. In case 4 the distention of the veins was so marked as to cause flattening of the endothelium. The walls of the veins, however, appeared to be normal and showed no evidence of inflammatory reaction. Although

11. Fahr, T.: Kreislaufstörungen in der Nieren, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1925, vol. 6, p. 132.

thrombosis of the main renal vein was found in only 2 cases, many microscopic thrombi were noted in the medulla near the hilus. This was particularly true in case 5, in which numerous thrombi were scattered throughout the medulla. The thrombus consisted of a mass of red cells, white corpuscles, much fibrin and agglutinated platelets. No organisms were noted in the thrombi or in the renal tissues.

COMMENT

Some authors have ascribed a greater predisposition to infarction and thrombosis to the left renal vein, on a purely anatomic basis. Thus, Osler and McCrae [12] stated that because of its greater length and because of the pressure exerted on it by the aorta, the left renal vein is more prone to thrombosis than the right. It is noteworthy that in 2 of our cases the right kidney was the seat of a thrombus and in 4 the right kidney was either totally or partially infarcted.

The frequent association of renal thrombosis with infarction of the kidney raises the question whether the infarction results from a thrombus in the main renal vessel or is brought about independently by a common etiologic factor. Oppenheim [13] expressed the belief that the basis for thrombosis in his cases was an injury to the capillary wall, which was followed by dilatation, diapedesis of red blood cells and extravasation of fluid elements into the intercellular spaces. He demonstrated with microscopic sections the progress from hyperemia to complete renal infarction without any evidence of thrombosis of the main renal vein. Similarly, in 3 of our cases in which there was renal infarction there was no thrombus in the main renal vein. In the 2 cases in which a renal thrombus was found there was no extension into the branches of the vessel.

Some comment should be made on the subject of the pathogenesis of renal infarction and thrombosis of the renal veins in the newborn. The question whether such factors as (1) predisposition of the newborn, (2) introduction of substances into the circulation which cause an increase in the agglutination of the blood, (3) polycythemia and anemia, (4) the effect of toxins on the walls of the veins, (5) dehydration and (6) infection play a role in the pathogenesis is still controversial and by no means settled.

The predisposition of newborn infants to venous thrombosis may be ascribed to the presence, at birth, of a lowered pressure in the venous

12. Osler, W., and McCrae, T.: Modern Medicine, Its Theory and Practice, ed. 2, Philadelphia, Lea & Febiger, 1914, vol. 3, pp. 789-790.

13. Oppenheim, F.: Ueber den haemorrhagischen Niereninfarkt der Säuglinge, Ztschr. f. Kinderh. **26**:192, 1920.

system corresponding to a condition of shock. This is possibly brought about, according to Perla,[14] by the diminution in the available adrenal cortical hormone, but this hypothesis does not explain the localization of a thrombus in the renal veins alone. It is believed that other factors which determine the site of the thrombus are the anatomic features which favor the slowing and eddying of the blood and the presence of any disease which will produce hemoconcentration and sluggish circulation. Although the decreased rate of flow in the newborn infant, as pointed out previously, is uniform throughout the entire vascular system, the rate in the kidney is further diminished by the nature of the renal circulation. This organ has a special type of circulation, in which the arterial blood passes through a long capillary network in the glomeruli before reaching the venous capillaries. There is little or no anastomosis of the renal vessels. Moreover, any retardation of the blood flow or impairment of oxygenation may lead to cloudy swelling of the tubules, which causes compression of the capillaries with further retardation of the venous circulation.

Some writers have expressed the belief that the cellular elements of the blood may form a solid mass within the vessels and block their lumens, independently of the clotting process. This usually occurs after a transfusion of incompatible blood, when the red cells become agglutinated into larger clumps and are lodged in the smaller vessels. Such a possibility, indeed, might be considered in view of the fact that our patients received one or two transfusions during the course of their illnesses. However, the absence of such urinary symptoms as anuria or hematuria, which are usually associated with the hemolysis following a faulty transfusion, excludes this factor as a cause. Aside from blood transfusion, no intravenous therapy which might cause agglutination was employed.

Polycythemia and anemia, which are so emphasized as factors in thrombus formation in the case of adults, cannot be considered in our cases. Polycythemia is a physiologic phenomenon during the neonatal period and during this period does not result in the same tendency for the blood to clot as it does at an older age. It is to be noted that in these infants diarrhea developed early in the neonatal period, the time at which the prothrombin in the blood is at the lowest level. There were no instances of severe anemia among the infants studied.

It has been suggested that either endogenous or exogenous toxins may produce a thrombus by damaging the endothelium of some of the blood vessels. Thus, Oppenheim [13] expressed the opinion that increased clotting was due to toxemia. The possibility that a toxic factor was the sole cause of thrombosis can hardly be entertained, for numerous

14. Perla, D.: Personal communication to the authors.

instances are encountered in which infants suffering from profound toxemia show no evidence of vascular damage and renal thrombosis.

There is no doubt that diarrhea associated with marked loss of body fluids produces a profound alteration in the blood volume as well as in the blood elements themselves. There are a marked diminution of blood plasma, an increase in the viscosity of the blood, due to hemoconcentration, and a loss of electrolytes. These changes in the circulation constitute a valid cause for thrombus formation. For that reason, the proponents of the marantic origin of thrombosis, as well as those supporting the theory of infectious origin, have emphasized that such thrombi develop only in cases of severe gastroenteritis with intoxication. In this connection, we refer to Hutinel,[15] who pointed out that the renal veins of newborn infants with diarrhea are predisposed to thrombosis as a result of the alteration in the blood, the hemoconcentration and the stagnation and not of pathologic changes in the walls of the veins. It is of interest to note that in the cases in which the diarrhea was complicated by renal thrombosis there were a marked loss in weight and dehydration, although the latter was not a conspicuous symptom in the rest of the cases.

Infection seems to have played a definite role in thrombus formation. Postmortem examination revealed interstitial pneumonia in 2 cases and middle ear infection in 3. It is of interest to recall that Hamburger [16] expressed the belief that in cases of gastroenteritis there is an increased permeability of the intestinal wall to viruses or their products, which may result in venous thrombosis. In the light of this suggestion, attention should be called to our previous paper,[10] in which it was pointed out that epidemic diarrhea may be of virus origin. Sections of the lungs in our cases showed changes similar to those in the cases of virus pneumonia of Rivers [17] and Goodpasture and associates.[18] Frühwald [19] was among the first to point out that infection plays an important role. Finkelstein [20] found streptococci in the thrombi in his cases and expressed doubt that marasmus is responsible for thrombus formation.

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15. Hutinel, V.: Les maladies des enfants, Paris, Asselin & Houzeau, 1909.

16. Hamburger, R.: Ueber Gefässthrombosen junger Kinder, Jahrb. f. Kinderh. **91**:439, 1920.

17. Rivers, T.: Personal communication to the authors.

18. Goodpasture, E. W.; Auerbach, S. H.; Swanson, H. S., and Cotter, E. F.: Virus Pneumonia of Infants Secondary to Epidemic Infections, Am. J. Dis. Child. **57**:997 (May) 1939.

19. Frühwald, F.: Haemorrhagischer Infarkt beider Nieren nach Cholera infantum, Jahrb. f. Kinderh. **23**:425, 1885.

20. Finkelstein, H.: Lehrbuch der Säuglingskrankheiten, Berlin, Julius Springer, 1921.

Czerny and Moser [21] also found bacteria in the renal thrombi. That a thrombosis of an arterial vessel may also result from sepsis or infection is brought out by the case reported by Feldstein and Goldstein,[22] in which the mesenteric thrombosis occurred in a child suffering from chronic suppurative mastoiditis. The thrombus was lodged in the three branches of the superior mesenteric artery. In cases of cerebral sinus thrombosis, chronic infection of the middle ear or mastoid is considered the most important etiologic factor.

It is obvious from the foregoing discussion that more than one factor must be taken into consideration. To what extent each factor is responsible for the pathologic condition we are unable to state, in the light of present knowledge. One must assume that an interrelation exists between the various factors. The striking similarity in the histories and in the physical and postmortem findings of the 5 cases suggests a similar underlying etiologic factor.

SUMMARY

The data in 5 cases of renal thrombosis with infarction complicating infectious diarrhea of the newborn are presented.

The pertinent literature on the subject is reviewed, and the possible pathogeneses are discussed.

Attention is called to the frequent occurrence of this complication in newborn infants during the course of epidemic diarrhea; 5 of the 25 infants on whom autopsy was performed had this type of renal complication.

The difficulty of diagnosing this condition during the course of the illness, because of the lack of urinary symptoms, is emphasized.

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21. Czerny, A., and Moser, P.: Klinische Beobachtungen an magendarmkranken Kindern im Säuglingsalter, Jahrb. f. Kinderh. **38**:430, 1894.

22. Feldstein, G. J., and Goldstein, J. H.: Mesenteric Thrombosis, J. Pediat. **8**:720, 1936.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

COMPARATIVE DIGESTIBILITY OF SOME SOFT CURD MILKS IN VITRO. F. J. DOAN and C. C. FLORA, Bulletin 380, Pennsylvania Agriculture Experiment Station, April 1939.

The study was carried out primarily to determine the accuracy of the measurement of curd tension as an index of the digestibility of various types of milk. The authors devised a new in vitro method of peptic digestion of milk. The in vitro results were compared with in vivo results, which were obtained by feeding rats identical samples. Various periods were allowed for digestion in vitro and before the rats were killed. The nitrogen content of the remaining curd was used to measure the completeness of digestion.

The authors found that the digestibility of untreated and of pasteurized milks appears to be in inverse proportion to their curd tensions. The same principle was demonstrated for evaporated milk, acidified milk and milk subjected to base exchange. Homogenized milk did not conform to this principle; it had a low curd tension, but its digestibility was not facilitated in proportion to the reduction in curd tension. Enzyme (trypsin)-treated milk was more easily digested than would be anticipated from the reduction in curd tension.

The size of curd particles was determined in the in vitro and in vivo samples by screening. The data showed that the particles were small in all milks in which modification facilitated digestion.

The authors concluded that in all probability the size of curd particles is a more accurate index of digestibility than is curd tension.

ZELDES, Chicago.

AN EVALUATION OF ENZYME TREATED MILK IN INFANT FEEDING. MAURICE L. BLATT, ELLIS H. HARRIS, HOWARD M. JACOBS and MARY ZELDES, J. Pediat. **17**:435 (Oct.) 1940.

The curd tension of cow's milk treated with a pancreatic proteolytic enzyme prior to pasteurization is reduced to such a degree that boiling is unnecessary. The curd formed from milk so treated is soft, flocculent and finely divided and does not tend to agglomerate. Elimination of boiling of milk simplifies the process of making formulas and reduces the danger of bacterial overgrowth from contaminants.

Newborn, premature and normal infants tolerated this milk well, developed normally and were found to have less diarrhea and infection of the upper respiratory tract than those in a like environmental situation given control milk.

RAUH, Cincinnati

A STUDY OF THE NUTRITIONAL AND PHYSICAL STATUS AND THE RESPONSE TO EXERCISE OF SIXTEEN NEGRO BOYS 13 TO 17 YEARS OF AGE. FREDERIC W. SCHLUTZ, MINERVA MORSE, DONALD E. CASSELS and L. VIVIAN IOB, J. Pediat. **17**:466 (Oct.) 1940.

A group of 16 Negro boys 13 to 17 years of age were "studied as to nutritional status, physical status, including lung volume and its subdivisions, blood and 'available fluid' volumes, basal oxygen consumption, heart rate, and blood pressure, and response to exercise, including both cardiovascular and blood changes." The results of these studies were compared with those found by Robinson, who studied a similar group of white children, in respect to physical fitness.

RAUH, Cincinnati.

EXPERIENCE WITH BENZEDRINE [AMPHETAMINE] SULFATE IN THE MANAGEMENT OF OBESITY IN CHILDREN. RALPH H. KUNSTADTER, J. Pediat. **17**:490 (Oct.) 1940.

Amphetamine sulfate was administered to 30 obese children between 2½ and 16 years of age. These children were selected after they failed to lose weight on a prescribed reducing diet and in some instances after thyroid therapy. The average weekly weight loss of 26 patients who received continuous treatment for more than two weeks was 0.831 pounds (377 Gm.) per week. The greatest loss of weight occurred during the first two weeks of treatment. There was little or no variation in the basal metabolic rate during amphetamine treatment. The effect of the drug on the pulse rate and on the blood pressure was variable and in most cases only slight. In 2 patients a marked bradycardia developed. Although 40 per cent of the patients experienced unpleasant reactions at the onset of treatment, it was necessary to stop administering the drug in only 4 instances because of severe reactions. The optimal effective dose of amphetamine sulfate for obese children was found to be between 10 and 30 mg. daily. Loss of weight was due primarily to loss of appetite and decrease in intake of food. Withdrawal of administration of the drug or decrease in the dose resulted in a return of appetite and an increase in weight. Tolerance to the drug developed frequently, requiring gradual increase in the dose. Kunstadter expresses the opinion that amphetamine therapy is an effective adjunct in the management of obesity in children, but social and psychologic adjustments, including improvement of eating habits, should be included in the treatment in an effort to reduce the intake of food following the withdrawal of the drug therapy.

RAUH, Cincinnati.

MILK: THE ROLE OF MEDICAL MILK COMMISSIONS IN DEVELOPING STANDARDS FOR MILK PRODUCTION. EDWARD S. RIMER, New York State J. Med. **40**:741 (May 1) 1940.

The history of the development of certified milk is well reviewed, and the work of certified milk commissions is described. "Certified Milk stands highest of all milks in vitamin and nutritional values and is cleaneast, purest, freshest, and most palatable." It is the only raw milk that is safe to drink. It is found that dairymen and groups of physicians will cooperate in establishing high standards of milk production and that the public is willing to pay more for milk produced according to such standards. Certified milk has been of great value in reducing infant mortality due to diarrheal diseases.

AIKMAN, Rochester, N. Y.

BLOOD UREA AND UREA CLEARANCE. F. MORTON and A. M. NUSSEY, Lancet **1**:637 (April 6) 1940.

The object of this study was to observe the effect of a large dose of urea on the clearing capacity of the kidneys. Fifty normal subjects and a small series of patients with evidence of renal disease were investigated.

The results confirmed previous observations that the Van Slyke technic often yields for normal subjects clearance values well below the accepted standards. These abnormally low values were found to disappear after the ingestion of urea.

Patients with definite renal disease seemed to show a fall or no change in clearance after taking urea, whereas patients with mild involvement showed a rise.

The level of blood urea was found to be relatively stable between three-fourths and one and three-fourths hours after urea was taken.

LANGMANN, New York.

PSYCHIATRIC COMPLICATIONS OF HYPOGLYCEMIA IN CHILDREN. E. W. ANDERSON, Lancet **2**:329 (Sept. 14) 1940.

Hypoglycemia, whether due to overdosage of insulin, to hyperplasia or neoplasm of the islets of Langerhans or to any other cause, shows itself most in symptoms referable to the nervous system. Among these have been listed nervousness, sweat-

ing, pallor, tremor, sleepiness, salivation, diplopia, muscular twitching, hemiplegia and jacksonian or epileptiform attacks. Psychic disturbances that sometimes accompany the neurologic signs include fears, anxieties, mild depression, faulty concentration, fugues and hallucinations.

Two cases of hypoglycemia with neuropsychiatric symptoms are reported, in which the patients were diabetic boys who became demented after an excessive dose of insulin.

LANGMANN, New York.

ACTION OF SODIUM CHLORIDE IN INFANTS. LUCEIN GAROT, O. GULKO and C. GOTTSHALK, Rev. franç. de pédiat. **14**:545, 1938.

Twelve infants under 6 months of age were studied. Six were given 1 Gm. of sodium chloride per kilogram of body weight each day for four days, and 6 were given half this amount. There was considerable individual variation in response. The authors summarized their observations as follows:

1. No consistent relation was observed between sodium chloride retention and hydration.

2. The body of the infant retained a part of the salt ingested. This retention varied from a few centigrams to several grams without any fixation of water in the great majority of cases. The retention of sodium and of chloride ions was not always in the ratio of sodium chloride, 0.64. In certain cases there was a profound dissociation of the salt, as the ratio of sodium to chloride retention varied from 0.45 to 1.88.

3. Variations in diuresis and in perspiration were noted, but these followed no definite rule.

4. Large doses of sodium chloride produced fever and an arrest of growth. Smaller doses seemed to have a favorable action on growth.

5. The elimination of large quantities of sodium decreased the excretion of potassium.

LESLIE, Evanston, Ill.

PROBLEM OF PERMEABILITY IN INFANTS. FRANZ GOLDMANN, Jahrb. f. Kinderh. **149**:365 (Aug.) 1937.

The author states that the premature infant has a tendency to retain the sodium ion. In the first half of pregnancy the body of the fetus has a relatively high content of sodium and chloride ions; at the end there is a relative increase in potassium. He also states that the fetus is richer in chloride than the newborn child, who in turn is relatively richer in chloride than the older child.

His studies showed a relatively high sodium ion retention in children classified as having the exudative diathesis. There were relatively high values for the sodium ion in the blood of children who suffered from alimentary intoxication.

LANDAU, Hannibal, Mo.

DILUTION OF BREAST MILK WITH WATER AND ITS DETECTION. J. STRÖM, Nord. med. **2**:1938 (June 24) 1939.

Determination of the fat content of breast milk by means of an ordinary butyrometer and of the specific gravity and correlation of these two values was used as a method of detection of falsification of breast milk by dilution with water. The sensitivity of the method depends on the fat content of the milk. The higher the fat content (low specific gravity), the more sensitive is the method and vice versa. In the most favorable cases even the slightest addition of water can be demonstrated; in other cases an addition of water up to 32 per cent is required in order to be demonstrable.

WALLGREN, Göteborg, Sweden.

SPONTANEOUS HYPOGLYCEMIC REACTIONS. S. WENDT, Svenska läk.-tidning. **36:** 1025 (May 19) 1939.

Four cases of spontaneous hypoglycemic reactions in children 1½ to 4 years of age are reported. The characteristic features are drowsiness, somnolence, uneasiness, tonic and clonic seizures occurring early in the morning and hypoglycemia. It is recommended to give slowly resorbing carbohydrates at the evening meal.

WALLGREN, Göteborg, Sweden.

Vitamins; Avitaminoses

ENDEMIC RIBOFLAVIN DEFICIENCY IN INFANTS AND CHILDREN. TOM D. SPIES, WILLIAM B. BEAN, RICHARD W. VILTER and NELWYN E. HUFF, Am. J. M. Sc. **200:**697 (Nov.) 1940.

Repeated clinical, laboratory and dietary studies of 241 infants and children having characteristic riboflavin deficiency have convinced the authors that it is the most common clinical deficiency disease among infants and children in an area in Alabama in which deficiency diseases are endemic. The mothers of these children usually subsisted on inadequate diets during pregnancy and lactation, and specific treatment of the mother with riboflavin or substances rich in riboflavin was curative for the lesions in the nursing infant.

The studies indicate that riboflavin deficiency is a noncontagious, nonhereditary disease which occurs in either sex of any race. It develops over months and years, and the appearance of diagnostic lesions is preceded by a period of ill health which should properly be termed the deficiency development time.

The response to specific therapy is gratifying; in every case the condition was relieved by the judicious use of one of the specific therapeutic agents. Following therapy an increase in vigor, a sense of well-being and in many instances a striking increase in growth occur. The ocular manifestations disappear, and the lesions around the mouth heal. As such lesions heal it becomes impossible to demonstrate the presence of Staphylococcus aureus hemolyticus and Streptococcus hemolyticus, which were prevalent before therapy.

The morbidity rate is greatly decreased when the physician makes the diagnosis early and initiates therapy. The authors found that in the average case the condition responds satisfactorily to the oral administration of 1 mg. of riboflavin three times a day or to 1 ounce (28 Gm.) of brewers' yeast or liver extract daily. These substances have been given for a sufficient time to warrant no hesitancy in recommending them as safe and effective therapeutic agents for the treatment of mothers and children. Despite the fact that the lesions of riboflavin deficiency were relieved while the general diet remained the same, the addition of liver, lean meat and milk to the diet is recommended whenever possible.

HENSKE, Omaha.

THE INFLUENCE OF LIVER DAMAGE ON THE PLASMA PROTHROMBIN CONCENTRATION AND THE RESPONSE TO VITAMIN K. S. P. LUCIA and P. M. AGGELER, Am. J. M. Sc. **201:**326 (March) 1941.

No significant correlation was found to exist between the results of the hippuric acid test for hepatic function and the prothrombin concentration in the plasma either before or after the administration of vitamin K. Patients with severe impairment of hepatic function, as demonstrated by the hippuric acid test, may at the same time have a normal prothrombin concentration. Prothrombin concentration may be elevated to normal after the administration of vitamin K, despite markedly impaired hepatic function.

"Failure to recover from hypoprothrombinemia following the administration of vitamin K cannot be correlated with the degree of impaired liver function as shown by the hippuric acid test.

"Regardless of the results of liver function tests, it has been found that: (*a*) In acute diseases of the liver, such as acute hepatitis and acute yellow atrophy, the fluctuations in the prothrombin concentration are conditioned by the severity of the illness and are not ordinarily influenced by the administration of vitamin K. (*b*) In chronic diffuse diseases of the liver, such as portal cirrhosis, there may be a low prothrombin concentration which is usually not elevated following the administration of vitamin K. (*c*) In obstructive jaundice, there may be a low prothrombin concentration which usually can be significantly elevated by the administration of vitamin K. When obstructive jaundice is complicated by severe liver damage, the response to vitamin K may be limited."

HENSKE, Omaha.

STUDIES IN THIAMIN EXCRETION. VICTOR A. NAJJAR and L. EMMETT HOLT JR., Bull. Johns Hopkins Hosp. **67**:107 (Aug.) 1940.

The authors have studied the daily excretion of thiamine in the urine of patients at different ages, including normal persons and patients with pathologic conditions. They also performed a thiamine excretion test in these subjects and studied the disappearance rate of thiamine from the blood serum after an intravenous dose. They find that normally there is a wide range of excretion depending on the thiamine intake. The result of a thiamine excretion test must be interpreted with caution because it may be complicated by renal function and other deficiency. No conclusions can be made concerning the behavior of serum thiamine following an intravenous injection.

LYTTLE, New York.

THE RELATION OF VITAMIN D INTAKE TO THE AGE OF THE INFANT AT THE TIME OF ERUPTION OF THE FIRST DECIDUOUS INCISOR. THOMAS D. SPEIDEL and GENEVIEVE STEARNS, J. Pediat. **17**:506 (Oct.) 1940.

"The ages at eruption of the first deciduous lower central incisor of groups of healthy infants with carefully controlled diets having relatively low, intermediate, and high amounts of supplementary vitamin D were compared.

"The incisors of twenty-two infants given the intermediate vitamin D intake, from 300 to 400 (U. S. P.) units daily, showed the earliest mean age at eruption, 24.68 weeks. The incisors of seventeen infants with a low vitamin D intake, from 135 to 270 (U. S. P.) units daily, were delayed in their eruption, appearing at a mean age of 28.29 weeks. Incisors of six infants with a high vitamin D intake, over 1,800 (U. S. P.) units daily, also seemed delayed in their eruption, appearing at a mean age of 27.16 weeks; however, this is less conclusive because of the small number of infants in this group.

"In an effort to determine whether early or late eruption is more nearly normal, the dental eruption data of six infants who had the 300 to 400-unit intake but who were subject to illnesses were presented. Although the group is small, the mean age of incisor eruption, 29.0 weeks, seemed to indicate that illness delays tooth eruption and that the earlier eruption age is more nearly normal.

"The response of dental eruption to variation in vitamin D intake tends to parallel the responses of linear growth and mineral retention to the same influence during infancy."

AUTHORS' SUMMARY.

POTENCY OF VITAMINS D_2 AND D_3 IN OSTEOMALACIA AND LATE RICKETS. DAGMAR CURJEL WILSON, Lancet **1**:961 (May 25) 1940.

"The therapeutic effects of pure specimens of vitamin D_3 (calciferol from irradiated ergosterol and of vitamin D_3 from irradiated 7-dehydrocholesterol were compared in thirteen pairs of patients with osteomalacia and in two pairs with late rickets among Indians, aged 6—70, in the Kangra valley, Punjab."

The two preparations proved equally effective.

LANGMANN, New York.

STERILIZATION AND OXIDATION OF ASCORBIC ACID. G. MOURIQUAND, H. TETE and P. VIENNOIS, Presse méd. **48**:553 (May 29-June 1) 1940.

It has long been known that canned lemon juice contains ascorbic acid enough to prevent scurvy, whether or not it has been previously sterilized. The authors found that on exposure to air, sterilized lemon juice lost its ascorbic acid content rapidly during the first week, but then the level remained only slightly below that of uncooked juice similarly exposed to air. In experiments with pure ascorbic acid instead of lemon juice, the unsterilized solution lost its ascorbic acid content much more rapidly and more completely. Since the p_H did not vary perceptibly, the phenomenon could not have been caused by a lowering of p_H following sterilization. Therefore the cause must be the loss of oxygen during sterilization. Theoretically, sterilized lemon juice, with its lower content of oxygen, should keep its ascorbic acid longer, but this is not the case. Sterilization, therefore, must destroy some protective substance in the juice, the lack of which allows more rapid oxidation. This observation is of practical value in that sterilized juices after exposure to the air must be consumed within a short time and while in the can must be protected from oxygen.

DAFFINEE, Boston.

THE TREATMENT OF RICKETS WITH IRRADIATED ERGOSTEROL. H. BISCHOFF, Jahrb. f. Kinderh. **150**:1 (Sept.) 1937.

The successful treatment of rickets and spasmophilia with irradiated ergosterol (concentrated vigantol) is reported. Early clinical, chemical and roentgen improvement was found. No adverse symptoms resulted.

LANDAU, Hannibal, Mo.

INVESTIGATIONS ON VITAMIN C METABOLISM IN LACTATING WOMEN; DEGREE OF PHYSIOLOGIC AND PATHOLOGIC SATURATION OF HUMAN ORGANISMS WITH VITAMIN C. THEOPHIL BAUMANN, Jahrb. f. Kinderh. **150**:193 (Nov.) 1937.

Among important data disclosed by the author's extensive investigations is the fact that the vitamin C content of human milk shows distinct seasonal variations, dependent on the vitamin saturation of the organism.

The minimum requirement of vitamin C in infancy lies between 8 and 17 mg. per day. This requirement is met by the current practice of administering fresh fruit and vegetable juices.

LANDAU, Hannibal, Mo.

T-FACTOR: ITS EFFECT ON THROMBOCYTOSIS. E. SCHIFF and C. HIRSCHBERGER, Jahrb. f. Kinderh. **150**:247 (Nov.) 1937.

The authors obtained results which were at variance with their previous findings regarding the thrombocytogenic factor in sesame oil. The investigations are to be continued.

LANDAU, Hannibal, Mo.

REQUIREMENT OF VITAMIN C BY INFANTS AND BY CHILDREN. H. RIETSCHEL, Kinderärztl. Praxis **11**:58 (Feb.) 1940.

It takes from four to seven months for scurvy to develop in human beings when their diet is devoid of vitamin C. Rietschel observed for over five months 2 adults whose ascorbic acid level in the blood had been decreased to zero in this fashion. They showed no symptoms of scurvy or of prescurvy. The usual assumption that human breast milk contains from 4 to 6 mg. of ascorbic acid per hundred cubic centimeters is not correct. The average values of ascorbic acid in breast milk obtained from women of the working classes were not more than 1 or 2 mg. per hundred cubic centimeters. Apples have the poorest content of vitamin C of all fruits. Rietschel begins to administer fruit juices to infants at the age of 4 months. He has not observed any incidence of scurvy or of prescurvy.

HEYMANN, Cleveland.

HIPS AS A SOURCE OF VITAMIN C. B. HAMMAR, Nord. med. **1**:702 (March 11) 1939.

The hips should be crushed and extracted in ordinary water at room temperature for five to ten minutes and then boiled for ten to fifteen minutes. In this way most of the ascorbic acid is extracted. WALLGREN, Göteborg, Sweden.

Prematurity and Congenital Deformities

"SPINAL DYSRAPHISM": SPINA BIFIDA AND MYELODYSPLASIA. BEN W. LICHTENSTEIN, Arch. Neurol. & Psychiat. **44**:792 (Oct.) 1940.

The author has written an excellent paper on the large group of disorders included under the general term spina bifida, stressing the developmental and pathologic phases of the condition. BEVERLY, Chicago.

VISCERAL PAIN IN CASES OF SITUS INVERSUS. ARTHUR B. KING, Bull. Johns Hopkins Hosp. **68**:169 (Feb.) 1941.

A study of the records of 79 patients in the literature and of 2 patients of his own with complete situs inversus and visceral pain led the author to advance the theory that the peripheral nerve routes may or may not be transposed independently of the viscera, the rotation occurring about 50 per cent of the time. When transportation does occur both viscera and pain pattern are reversed but in cases of nonrotation of the nerve pathways the pain pattern remains in its usual location.

A SYNDROME CHARACTERIZED BY ECTODERMAL DYSPLASIA, POLYDACTYLY, CHONDRODYSPLASIA AND CONGENITAL MORBUS CORDIS. RICHARD W. B. ELLIS and S. VAN CREVELD, Arch. Dis. Childhood **15**:65 (June) 1940.

A syndrome consisting of ectodermal dysplasia affecting the hair, nails and teeth, polydactyly, chondrodysplasia and congenital morbus cordis is described. No detailed account of this syndrome has been found in the literature. The full syndrome was observed in 2 children, and a third child showed all the components except hypotrichosis and congenital morbus cordis. Two of the patients were girls, and 1 was a boy. They were of English, Dutch and Jewish-American descent respectively. In 2 of the 3 cases the parents were first cousins. No similar condition had been observed among relatives. The condition is held to be a mendelian recessive characteristic, without sex linkage. KELLY, Milwaukee.

EXTROVERSION OF THE PRIMITIVE HIND GUT. J. EDGAR MORISON, Arch. Dis. Childhood **15**:105 (June) 1940.

"A case is described of ectopia of the bladder associated with an opening into the bowel from the subumbilical part of the abdominal wall. The mechanism of development of the gut behind the vitelline duct is discussed, and apart from a small blind tube growing into the dorsal mesentery this part of the bowel is considered to be absent. The opening of the primitive hind gut is considered to result from the failure over almost its entire extent, of the primitive line of junction of ectoderm and endoderm forming the cloacal membrane, to be invaded by mesoderm. This probably resulted from a deficient formation of mesoderm at the hind end of the primitive streak." KELLY, Milwaukee.

A CASE OF CONGENITAL HEMIHYPERTROPHY. J. SIMIAN and M. SCHACHTER-NANCY, Rev. franç. de pédiat. **13**:187, 1937.

A case is reported. The hypertrophy involved the muscles of the right arm, buttock, thigh and leg. The left thigh and leg also appeared somewhat larger than normal, but not so large as the right. The child had been born prematurely. LESLIE, Evanston, Ill.

A Peculiar Case of Cleidocranial Dysostosis in a Child of Seven. Hildegard Winkler, Jahrb. f. Kinderh. **149**:238 (July) 1937.

A classic case of cleidocranial dysostosis is described in detail. Photographs and roentgenograms are reproduced. The various etiologic theories are presented, and their weak points are exposed. The author states that Visellefont's idea of a hypophysial lesion must be considered a possibility in this case because of the enlarged sella turcica as shown by roentgen examination. The child was considerably shorter than the average.

Landau, Hannibal, Mo.

Familial Total Situs Inversus. Haakon Natvig, Nord. med. (Norsk mag. f. lægevidensk.) **1**:681 (March 11) 1939.

Two sisters, respectively 9 and 6 years of age, with total situs inversus but without congenital heart disease or other congenital anomalies are described. The parents, the grandparents and 5 siblings did not show any transposition. In Norway 25 cases of situs inversus have been reported, and, according to Berner, one may reckon with 1 case in 2,300 necropsies. Cases of familial situs inversus have been observed 8 times, once before in Norway (Frölich) and once in Sweden (Mattisson).

Wallgren, Göteborg, Sweden.

Care of Premature Babies. G. Lindberg, Nord. med. (Hygiea) **2**:1273 (April 29) 1939.

An incubator similar to that indicated by Moll (a canvas tent heated by electric bulbs) is recommended. The infant remains undressed in this tent until its weight has reached 2,000 Gm. The tent is equipped with a regulated permanent oxygen supply, and the humidity level of the room is kept at about 65 per cent. The babies are fed by means of catheters six times a day until they are able to nurse.

Wallgren, Göteborg, Sweden.

Newborn

Factors Influencing Plasma Prothrombin in the Newborn Infant. A. E. Maumenee, L. M. Hellman and L. B. Shettles, Bull. Johns Hopkins Hosp. **68**:158 (Feb.) 1941.

This study shows that the incidence of retinal hemorrhage in newborn infants can be reduced through the administration of vitamin K to mothers during labor. The incidence of retinal hemorrhage in infants of untreated mothers was 25 per cent and in infants of treated mothers 15 per cent. It was also found that the administration of vitamin K to mothers prior to the onset of labor almost entirely eliminates retinal hemorrhage in their infants.

Lyttle, New York.

Prothrombin in the Newborn Infant: Relationship to the Maternal Dietary Vitamin K Intake. Simon Kove and Henry Siegel, J. Pediat. **17**:448 (Oct.) 1940.

The prothrombin clotting time of 76 newborn infants was determined according to the method of Quick. Low prothrombin levels were found in 52 in the first eight days of life. Wide individual variations in prothrombin levels occur in each of the first eight days, but most commonly in the first two days. The average prothrombin level is at its lowest in the first two days and then rises slowly but remains below the normal adult value. A study of the dietary history of 68 of the 76 mothers failed to reveal any correlation between the maternal dietary vitamin K intake and the prothrombin concentration of the offspring. Kove and Siegel believe that food sources cannot be depended on to assure adequate prothrombin

levels in the newborn infant and recommend that vitamin K concentrate be given prophylactically to the mother before labor to assure elevated prothrombin levels in the newborn infant.

RAUH, Cincinnati.

DISTURBED RESPIRATORY FUNCTION IN THE NEWBORN AND YOUNG INFANT. DE LA B. FORTIER, Union méd. du Canada **69**:838 (Aug.) 1940.

Fortier discusses the physiologic aspects of respiration in the newborn. The fundamental characteristics may be modified by various conditions, particularly intracranial hemorrhage, atelectasis and thymic hypertrophy. Differential diagnosis and treatment are given in detail.

DAFFINEE, Boston.

THE CLINICAL PICTURE OF STAPHYLOCOCCAL INFECTIONS IN THE NEWBORN. JEAN M. CASS, Arch. Dis. Childhood **15**:85 (June) 1940.

The clinical types of staphylococcic infections of the newborn are reviewed, and the significance and prognosis of each type are discussed. The potential dangers of cutaneous lesions both to the infants affected and to those in contact with them is noted. It is found that newborn children react to staphylococcic infection in a characteristic manner, but, as in adults, the infection may be apparently completely localized, bacteremic or septicemic. The difficulty of making the diagnosis of staphylococcic meningitis and staphylococcic pneumonia during life, the relative values of clinical bacteriologic signs of staphylococcic septicemia and the absence of reports of cases of staphylococcic gastroenteritis in the newborn are discussed. Anemia is found to be a late and relatively mild complication of staphylococcic neonatal sepsis, but it persists until the infection is completely localized and may therefore persist long after the neonatal period.

KELLY, Milwaukee.

A CASE OF HYDROPS FOETALIS. J. V. O'SULLIVAN and J. R. GILMOUR, Brit. J. Child. Dis. **37**:119 (April-June) 1940.

A case of familial hydrops and erythroblastosis foetalis with pathologic changes is described. A short description of the usual features of this disease is appended.

LANGMANN, New York.

STUDIES ON AGGLUTININS AND AGGLUTINOGENS IN THE BLOOD OF THE NEWBORN. G. J. HALBRECHT, Brit. J. Child. Dis. **37**:175 (July-Sept.) 1940.

The mistaken opinion is widely held that an infant during the first month of life may be considered a universal recipient as far as transfusion is concerned, as his blood possesses no agglutinins.

One thousand newborn infants were examined at birth, and in no instance was there any difficulty in determining the blood group. In 53 per cent the blood was of the same group as that of the mother.

Two hundred newborn infants were examined for agglutinins, and 75 (37.5 per cent) were found to possess them.

Agglutinogens were invariably present in the red blood cells of the newborn after the seventh fetal month.

LANGMANN, New York.

GANGRENE OF THE NEWBORN. G. LÉVY, Nourrisson **28**:103 (May) 1940.

Two cases are described. The leg of 1 infant, 11 days old, had to be amputated below the knee; in the other infant a gangrenous area in the right gluteal region, 3 cm. in diameter, healed without surgical intervention. There is included a discussion of the pathology, cause, diagnosis and treatment of the condition.

HEYMANN, Cleveland.

REFLEX MOVEMENTS PRECEDING THE ACT OF SUCKING IN THE NEWBORN. F. STIRNIMANN, Jahrb. f. Kinderh. **149**:326 (Aug.) 1937.

The movements preceding the act of sucking in the neonatal period are influenced by many factors. These different movements are influenced by whether the infant is awake or asleep. They are also dependent on whether the infant is hungry or not.

LANDAU, Hannibal, Mo.

Acute Contagious Diseases

THE CONQUEST OF INFANTILE PARALYSIS. BASIL O'CONNOR, address read at the first annual meeting of the National Foundation for Infantile Paralysis.

The president of the National Foundation for Infantile Paralysis tells of the work and the expenditures of the Foundation. For the last two years 50 per cent of the funds raised was left in the locality in which the money was obtained, to be administered by the local chapter. The Foundation is carrying on studies in five fields: on the poliomyelitis virus, the relation of nutrition to poliomyelitis, after-effects of the disease, epidemiology and professional and lay education. Some particulars are given of the work in each field.

LESLIE, Evanston, Ill.

SMALLPOX IN THE AMERICAN WAR OF INDEPENDENCE. HUGH THURSFIELD, Ann. M. Hist. **2**:312, 1940.

At the onset of the War of Independence smallpox was a familiar disease in America, especially among the Negroes of the South, but was not as universal as in Europe. It exercised a profound influence on the American armies.

In 1775 General Howe occupied Boston. He was unable to attack the Americans on the surrounding hills because of a smallpox epidemic in Boston, which to some extent affected his troops. When he evacuated the town early in 1776, Washington sent there only 1,000 men, who had had the disease, as he greatly feared a spread of the disease through his army.

In order to anticipate a surprise by the Canadians, Washington sent a small force up the St. Lawrence River. After some small successes the Americans tried to take the then weak town of Quebec in Canada. A siege of this town was unsuccessful because of an outbreak of smallpox. In May 1776, 900 of a force of 2,000 were sick, mostly with smallpox. The siege was raised, and the force retreated to Crown Point, on Lake Champlain. The mortality was enormous. The author expresses the belief that smallpox was mainly responsible for saving Canada for the British Empire.

By 1777 smallpox was spreading so much that Washington decided on inoculation of all members of the army who had not had the disease. Prior to the war, his own native state, Virginia, had enacted a law making inoculation a penal offense. He was willing to accept the disadvantages and inconveniences, for he felt that this step was absolutely necessary, because "should the disorder infect the army in this natural way . . . we should have more to dread from it than from the sword of the enemy." The necessary resolution was passed by Congress, and the soldiers were inoculated in batches. The smallpox mortality at that time was over 16 per cent, but from the disease produced by inoculation only about 1 in every 300 died, and some regiments of 500 were inoculated without a loss. Besides, this measure removed the main obstacle to recruiting.

It seems that the immunization of the army was a factor of tremendous importance in bringing about the American victory in the War of Independence.

Quotations from one of the earliest books on military medicine, "A View of the Diseases of the Army," by Thomas Dickson Reide, published in 1793, show that inoculation was considerably practiced in the English army and that some regiments remained free from the disease through many campaigns.

ROSENTHAL, St. Paul.

NEUROLOGIC COMPLICATIONS OF CHICKENPOX: REPORT OF TWO CASES. MABEL G. MASTEN, Arch. Pediat. **57**:749 (Dec.) 1940.

Two cases in which there were neurologic complications of chickenpox are reported. A review of the literature reveals that chickenpox is not an entirely innocuous ailment; the mortality from the disease is 0.4 per cent, and in 5.2 per cent of cases complications occur, 6 per cent of which are neurologic. Twenty-seven per cent of the patients with neurologic complications die or have some residual symptoms.

ORR, Buffalo.

SPECIFIC INFLAMMATION OF THE CORNEA IN CHICKENPOX. A. LOWENSTEIN, Brit. J. Ophth. **24**:391 (Aug.) 1940.

The author points out that vitiligo iridis has been observed after smallpox, experimentally from injected virus of herpes febrilis (herpes iridis usually occurring with relapsing hemorrhages into the anterior chamber) and after chickenpox. A case is reported in which specific keratitis and iritis occurred in the course of chickenpox. The following summary is supplied by the author:

"The previously unknown clinical picture of corneal infection with chickenpox virus is described, with slit-lamp pictures. An earlier observation of the author, who had found vitiligo iridis after chickenpox, is thus completed. The new recognised forms of vitiligo iridis in smallpox, chickenpox, herpes iridis (zoster), inoculation iritis in rabbits (herpes febrilis), and scarlet fever present a unity from which we can deduce a biological relationship between their germs."

The article is illustrated.

W. ZENTMAYER. [ARCH. OPHTH.]

ELEVEN YEARS OF DIPHTHERIA IMMUNIZATION IN A RURAL DISTRICT. G. NICHOLSON and AUDREY Z. BAKER, Brit. M. J. **2**:354 (Sept. 14) 1940.

This paper gives statistics and clinical notes on a program of immunization against diphtheria carried out over an eleven year period. The authors used alum-precipitated toxoid, and only one injection was employed for a short while. They finally adopted the method of administering two doses, with an interval of not less than a month between doses.

ROYSTER, University, Va.

THE VALUE OF VITAMIN B_1 IN DIPHTHERIA. G. E. DONOVAN and M. BANNISTER, Brit. M. J. **1**:359 (March 8) 1941.

Because of the similarity of symptoms incident to vitamin B_1 deficiency and diphtheria, particularly in the presence of circulatory failure and polyneuritis, the authors made an experimental study in which they investigated the effect of using vitamin B_1 in 20 cases of diphtheria; they checked the results by observations in 20 control cases. Their conclusions are that vitamin B_1 exercises neither a prophylactic nor a therapeutic effect on diphtheritic paralysis or the cardiovascular complications of diphtheria.

ROYSTER, University, Va.

NEW CHEMOTHERAPEUTIC TREATMENT OF EPIDEMIC MENINGITIS. KARL GREINER and ERIKA JURANY, Ann. pædiat. **156**:15 (Oct.) 1940.

Between 1938 and 1940 the authors treated 10 patients with meningococcic meningitis by chemotherapy: 3 with sulfanilamide, 3 with sulfapyridine (2-[paraaminobenzenesulfonamido] pyridine) and 4 with sulfathiazole (2-[paraaminobenzenesulfonamido] thiazole).

One of the patients treated with sulfanilamide died. In the other 2 cases the treatment was successful, but there were residual cerebral defects. The improvement was slow. In 1 case there was a relapse after four weeks of treatment.

All of the patients treated with sulfapyridine made complete recoveries and had no residual cerebral defects. Improvement was rapid, in contrast to that in the

cases in which sulfanilamide was used. The patients' minds were clear after two to six days, and the spinal fluid was sterile after five to eight days. During treatment toxic symptoms were observed; in 1 case there was damage to the liver and in another case severe anemia.

The 4 patients treated with sulfathiazole recovered consciousness after two to six days, the high fever dropping by crisis. The meningeal symptoms disappeared after seven to ten days, and the disease healed completely after two to three weeks without any remaining cerebral defect. No toxic symptoms were observed.

The use of chemotherapy in treating meningoccccic meningitis has been called a great advance by Sprockhoff and Hoppe. The use of sulfathiazole is recommended as a further step forward.

AUTHORS' SUMMARY.

TREATMENT OF MENINGOCOCCIC MENINGITIS WITH SULFAPYRIDINE. L. v. MONAKOW, Ann. pædiat. **156**:92 (Jan.) 1941.

Twenty-six cases may be a rather small number on which to decide about the usefulness of a therapeutic method. Nevertheless, the following statements can be made about the efficacy of sulfapyridine (2-[paraaminobenzenesulfonamido] pyridine) in cases of meningococcic meningitis:

(1) The mortality rate for patients treated in one hospital was lowered in the last ten years from 70 to 11.5 per cent.

(2) The course of the disease was relatively short. The healing effect of sulfapyridine was recognizable in a shorter time than that of serum treatment or of "prontosil." (The article does not state whether the original prontosil [the hydrochloride of 4-sulfamido-2',4'-diamenoazobenzene] or neoprontosil [azosulfamide, that is, the disodium salt of 4-sulfamidophenyl-2"-ago-7'-acetylamino-1'-hydroxynaphthalene-3', 6'-disulfonic acid] was meant.) There were no relapses.

(3) No residual damage to the nervous system was observed.

(4) Results even with infants were good.

On the other hand, the therapy had no effect in the cases in which there were grave circulatory defects, the so-called encephaloadrenal type. Complicating encephalitis seemed to be favorably influenced by blood transfusion.

In evaluating treatment in cases which were encountered in the course of only one year, the type of the disease occurring during that period has to be considered as well. However, the impression was not gained that the disease in these cases was particularly benign.

Serum treatment was avoided because of its dubious value.

AUTHOR'S SUMMARY.

EPIDEMIOLOGIC ASPECTS OF THE 1937 EPIDEMIC OF POLIOMYELITIS IN ZURICH. W. ABEGG, Ann. pædiat. **156**:115 (Jan.) 1941.

The course of an epidemic of poliomyelitis in 1937 was not connected with the school holidays, the rifle match of the boys, the biggest festival for children of the year, or the aviation meet. The portions of the city affected in one year remained free in the next. The mortality rate for children was 9.58 per cent, while that for adults was nearly twice as high. Ten and eight-tenths per cent of the children had some residual paralysis.

AUTHOR'S SUMMARY.

AURICULAR FLUTTER AFTER DIPHTHERIA. ALFRED BEER, Jahrb. f. Kinderh. **149**:207 (July) 1937.

A case of auricular flutter following diphtheria in a 9½ year old child is reported. The course was followed by the electrocardiograph, and the outcome was favorable.

After reviewing the literature and studying his own case, the author states that the factors responsible for the appearance of this condition are: (1) a fresh area

of myocarditis, (2) damage to bundle tissue in the region of the sinus node and (3) involvement of the sympathetic nervous system (because of the appearance at the time of the development of polyneuritis). LANDAU, Hannibal, Mo.

STATISTICS OF EFFICACY OF SERUM THERAPY IN DIPHTHERIA. HERST HABS, Jahrb. f. Kinderh. **149**:340 (Aug.) 1937.

The author feels that there is little doubt from a statistical study that patients treated with diphtheria antitoxin have a much lower mortality than those not treated in this manner. LANDAU, Hannibal, Mo.

Chronic Infectious Diseases

BRONCHIAL OBSTRUCTION IN PULMONARY TUBERCULOSIS IN CHILDREN, ITS RELATION TO EPITUBERCULOSIS. KORMEL TERPLAN and ELIZABETH HYDE, Am. Rev. Tuberc. (supp.) **42**:1 (Aug.) 1940.

Tuberculous infection of a bronchus may result from direct extension of a recent primary focus into its lumen by perforation by a bronchopulmonary lymph node. In such cases marked intrabronchial spread leading to progressive caseated pneumonia with secondary cavitation occurs. There are other cases, however, in which occlusion of the bronchi by the tuberculous process results in complete atelectasis of the corresponding lobe or lobule but not to further interbronchial spread to other parts of the lung. In such cases, those tuberculous lesions which do occur within these atelectatic areas are relatively insignificant. It appears that the tuberculous process in such cases may remain arrested within the lumen of a smaller bronchus and may completely heal, or at most it may result in atelectasis distal to the occluded bronchi. In such cases there seems to be no further spread of the tuberculous infection within the collapsed lung. Atelectatic immobilization, and possibly a relative lack of oxygen, inhibits the growth of tubercle bacilli and promotes fibrous organization. A series of 6 cases is presented in support of the authors' conclusion that epituberculosis is not a true tuberculous pneumonia which heals by resolution but an atelectasis caused by complete obturation of bronchial lumens with specific tuberculous structures. EUGENE H. SMITH, Ogden, Utah.

I. NOMENCLATURE AND ANATOMICAL METHODS. KORMEL TERPLAN, Am. Rev. Tuberc. (supp.) **42**:5 (Aug.) 1940.

This 176 page supplement, entitled "Anatomical Studies on Human Tuberculosis," merits careful study by every one who is interested in this disease. In these papers are analyzed the results of painstaking studies of the material obtained from 698 autopsies on children and 289 on adults. Detailed roentgenographic studies of undissected specimens, followed by anatomic dissection and complete histologic analysis of the lesions found, were made in each case.

To correct some of the confusion which now prevails in American literature with regard to the meaning of terms, Terplan holds that the following interpretations should be accepted:

A primary focus is the structural change or reaction of the tissues brought about by the tubercle bacillus at the site of the first recognizable localization.

The term primary complex should be used as originally applied by Ranke: it comprises the primary focus and the tuberculous lesions in the lymph nodes in close topographic relation to the focus.

The term reinfection should be used only in its strictest sense, that is, to refer to a new infection with tubercle bacilli from without, excluding any formal genetic relation to the primary infection. "Endogenous exacerbation" appears more correct than "endogenous reinfection" to describe reactivation and spreading from tuberculous lesions in lymph nodes in older complexes.

EUGENE H. SMITH, Ogden, Utah.

II. Incidence and Anatomical Types of Tuberculosis in Children. Kormel Terplan, Am. Rev. Tuberc. (supp.) **42**:14 (Aug.) 1940.

In autopsies on about 700 children and young adults between the ages of 1 month and 18 years tuberculous lesions were found in 5.9 per cent of those below 6 years of age, and in 19.4 per cent of those between 7 and 18 years of age. In all, such lesions were found in 57 cases, in 35 of which death was due to the tuberculous disease, which, with 2 exceptions, started in a primary pulmonary focus. The exceptions were the cases of a 4 week old infant with congenital tuberculosis and of a young child with primary intestinal tuberculosis. In 22 cases tuberculosis was an incidental finding, in 3 of which the intestine appeared to be the portal of entry, while in the remainder there was primary pulmonary invasion.

The whole group of 57 cases is divided into 15 catagories, which are discussed in detail, especially from the standpoint of histology and pathogenesis. In the largest group (23 cases) there was a primary complex in the lung and bronchomediastinal lymph nodes, with hematogenous dissemination. In all these cases dissemination apparently had followed lymphogenic extension within the primary complex. In all except 3 cases the process was one of so-called generalization in connection with a progressive caseated complex. In 21 of the 23 cases diffuse tuberculous meningitis was found, and in 1 of the other 2 cases, in which dissection of the head was restricted, there was definite clinical evidence of involvement of the central nervous system.

In 27 of the 30 cases for which the clinical data are discussed, the first symptoms of the tuberculous disease were those of tuberculous meningitis or were due to the presence of tubercles in the brain. The duration of these symptoms until the patient's death was from four to six weeks.

The value of this study, as of the others in this series, can be appreciated only by a careful reading of the original paper. Eugene H. Smith, Ogden, Utah.

III. Primary Tuberculous Pulmonary Foci Without Lymph Node Changes. Kormel Terplan, Am. Rev. Tuberc. (supp.) **42**:44 (Aug.) 1940.

Of the 5 cases reported in this paper, in 3 the primary focus was in a completely calcified state, with some marginal formation of bone, and in 2, multiple foci in calcified and chalky-fibrous states were distributed over all lobes, in 1 case numbering 13 and in the other 24. In the 5 cases all intrapulmonary and bronchomediastinal lymph nodes regional to all foci were examined in histologic serial sections, with negative results. Eugene H. Smith, Ogden, Utah.

Tuberculin Reactors and Exposure Cases. Joseph A. Johnson, Philip J. Howard, F. Janney Smith and Bruce H. Douglas, Am. Rev. Tuberc. **42**:551 (Nov.) 1940.

The scope of this paper is more clearly indicated in the subtitle, "A Follow-up Study of Cases Removed from Contact: An Enquiry Into Endogenous Reinfection." The material for study was a group of 828 children sensitive to tuberculin who were removed from contact to a supervised environment and followed for varying periods up to twelve years. In 33 of these children reinfection type tuberculosis developed, in 23 of the 33 after contact had been broken. From an epidemiologic standpoint, it is interesting to note that of these 828 positive reactors, 380 gave a definite history of exposure to tuberculosis ,and this group included 18, or 78 per cent, of the 23 children in whom reinfection type tuberculosis developed. In explanation of this observation it is reasonable to suppose that the children who were known to have been exposed to tuberculosis received larger and probably repeated doses of bacilli, which resulted in a more extensive infection and a much less stable healing process than in those who received a small dose from a casual exposure.

The quantitative estimations of sensitiveness to tuberculin made periodically showed fluctuations, for the most part unexplained, with a general tendency to decline. In 26 instances reaction was lost to 0.1 mg. of old tuberculin.

In discussing the various factors concerned in the activation of the tuberculous lesion, the authors suggest that the common denominator of these activating agents, which include diet, infection, growth and hormonal influences, is nutrition. They emphasize the unreliability of weight curves and food intake alone as measures of the nutritional status and requirements. Detailed in the paper are metabolic observations on a number of factors relating to the nutrition of the growing period which bring out (1) the high protein requirement of the growing child, (2) a correlation between negative nitrogen balance and failure of the disease to heal, (3) the depressing effect on the retention of nitrogen and calcium of the phenomena of puberty in the girl and (4) the similar effect of focal infections and of (5) abnormalities in the basal metabolic rate.

EUGENE H. SMITH, Ogden, Utah.

BCG VACCINE. ITS PREPARATION AND THE LOCAL REACTION TO ITS INJECTION. JOSEPH D. ARONSON, ERMA I. PARR and ROBERT M. SAYLOR, Am. Rev. Tuberc. **42**:651 (Nov.) 1940.

This study was conducted on various tribes of American Indians in various parts of the country, from Arizona to Alaska. In all, 1,565 persons, ranging in age from 1 to 19 years, were vaccinated intracutaneously, and approximately the same number were used as controls. Both groups were determined to be free from tuberculosis by cutaneous testing and roentgen examination.

The BCG employed was freshly prepared and was used within three days. Details of the preparation of the vaccine and its cultural and biologic characteristics are included in the paper.

From 0.1 to 0.15 mg. of BCG was injected intracutaneously. There were no untoward local or general reactions and no instances of abscess formation or ulceration of the regional lymph nodes. After one year 9.3 per cent of 1,481 persons were found to be sensitive to purified protein derivative; after two years 93.3 per cent of 1,446 and after three years 95.3 per cent of 619 reacted. The antigenicity of the vaccine appeared to be influenced by the rate of growth of the culture used but was not related to the age of the culture or to the number of generations of growth on a bile-free medium. Because of marked variations obtained by different investigators, it is suggested that the mode of preparation of the vaccine and the determination of the allergy induced be made uniform.

EUGENE H. SMITH, Ogden, Utah.

TUBERCULIN TESTING IN CHICAGO SCHOOLS. FREDERICK TICE, Am. Rev. Tuberc. **43**:96 (Jan.) 1941.

This survey was wide in scope; it included all types of schools and all economic levels. Only children in kindergarten and the first and eighth grades were tested routinely, but thousands of students attending high schools and miscellaneous educational institutions were also examined. Altogether, 167,345 children and adolescents were tested and 23,532 roentgenograms were taken. The total number reacting positively to purified protein derivative was 27,401. Among these, 218 cases of reinfection type tuberculosis were found at the first examination, 107 more in the follow-up of children suspected of having the disease, 226 through the follow-up of the contacts of tuberculin reactors in the home and 35 among teachers and school personnel, making a total of 586 cases in all.

The rather small number of new cases found in such an extensive survey seems to indicate that case finding among children is both expensive and unproductive. The estimated cost of each new case found was $450. The procedure of the future would seem to be a complete roentgenologic survey, including examination of men,

women and children, in areas of excessive mortality from tuberculosis. In such a survey the miniature x-ray film has stepped up to first place as a case-finding instrument.

EUGENE H. SMITH, Ogden, Utah.

LARYNGEAL TUBERCULOSIS IN AN INFANT. SHIRLEY HAROLD BARON, Arch Otolaryng. **33**:308 (Feb.) 1941.

The author presents the rare case of an infant, aged 2 years and 8 months, who had laryngeal tuberculosis.

GREENWOOD, Chicago.

EARLY GLOSSOEPIGLOTTIC CHANGES IN CONGENITAL SYPHILIS. F. GREGORINI, Arch. ital. di otol. **52**:318 (June) 1940.

Gregorini reports the observations made at autopsy on a child, aged 3 months, who died of acute bronchopneumonia. The significant changes were observed in the tongue and the epiglottis, the spleen and the liver. The mucosa of the base of the tongue was smooth, and the glossoepiglottic folds were absent; the epiglottis was shortened and rounded and thicker than normal. The absence of polynucleated leukocytes (lymphocytes were present) in the infiltration, the evidences of productive endoarteritis and periarteritis, the wide extension of the process, the lack of regenerative phenomena and the deformation indicate a syphilitic source of the inflammation.

Opinions as to the frequency of early syphilis of the larynx vary, probably because the symptoms are often unnoticed in infants or are overshadowed by other conditions.

DENNIS, San Diego, Calif. [ARCH. OTOLARYNG.]

FALSE POSITIVE REACTIONS IN THE SPINAL FLUID (SYPHILIS). ANTONIO SELLEK Y AKEJANDRO FRADE, Arch. de med. inf. **9**:184 (July-Sept.) 1940.

The problem of false reactions in hemolysis and flocculation tests for syphilis on the spinal fluid of patients suffering from such nonsyphilitic disorders as tumor of the brain, tuberculous and purulent meningitis, poliomyelitis and encephalitis has long been the subject of discussion. The author found that 9, or 18 per cent, of 50 patients with tuberculous meningitis had positive reactions to the Meinicke test, while positive reactions to both the Meinicke test and the Kahn test on the blood were elicited in only 1 instance. This led him to believe that such tests are worthless for diagnostic and differential diagnostic purposes. Therefore other cytologic reactions, such as the Lange reaction or hemolytic and flocculation tests on the blood serum, should be used instead of tests on the spinal fluid in such instances.

SANFORD, Chicago.

A GIANT TUBERCULOUS CAVITY IN AN INFANT. SÁNCHEZ SANTIAGO, RÁUL PEREIRAS, SOSA BENS and JUAN Y JIMÉNEZ, Arch. de med. inf. **9**:241 (Oct.-Dec.) 1940.

The immense cavity, which covered parts of two lobes, undoubtedly resulted from an infection acquired from the mother, who had tuberculosis. Artificial feeding and the poor condition of the infant decreased his powers of resistance.

SANFORD, Chicago.

NEW ASPECTS OF THE OLD PIRQUET REACTION (PROXIMAL HYPERERGIC REACTIONS). E. MAYERHOFER, Ann. pædiat. **156**:84 (Jan.) 1941.

In testing with tuberculin (Pirquet test) in the usual way—by introducing the substance first at a proximate and then at a distal point—one sees in fresh tuberculous processes a stronger reaction (reddening and swelling) at the proximal point. This can be explained as follows:

(1) There is a partial resorption of tuberculin from the distal point and in consequence an addition of tuberculin at the proximal point.

(2) There is a sensitization of the proximal point by the previous inoculation. The small quantities of tuberculin resorbed from the distal point produce a hyperergic reaction (*Frühreaktion*).

(3) In some cases there is a special readiness to react, which is most frequent in children with active tuberculosis.

Pirquet tests which give rise to such hyperergic reactions at the proximal point of inoculation should warn the physician to be careful in diagnosis and treatment. The observation of the phenomenon described is extremely simple for every practitioner.

AUTHOR'S SUMMARY.

Diseases of Blood, Heart and Blood Vessels and Spleen

CLINICAL OBSERVATIONS ON A CASE OF SPORADIC HEMOPHILIA. ROBERT DANZER, Jahrb. f. Kinderh. **150**:65 (Oct.) 1937.

A typical case of hemophilia in a 5 year old boy is reported. The family history was irrelevant; so this is classified as a case of sporadic hemophilia, or as the first appearance of the condition in this family.

LANDAU, Hannibal, Mo.

ENDOCARDITIS AND MYOCARDITIS IN NURSLINGS. ROBERT FELDMANN, Jahrb. f. Kinderh. **150**:138 (Oct.) 1937.

The paucity of reports of rheumatic heart disease in nurslings is stressed. In most cases cardiac disease in infancy (other than congenital heart disease) is the result of septic processes, although rheumatic infections do occur. The author presents reports of examples of cardiac involvement due to streptococcic sepsis with necrotic myocarditis, multiple congenital cardiac deformities with endocarditis, endocarditis lenta, and a case of cor bovinum from mitral disease in a 4 month old girl whose mother had rheumatic fever during pregnancy.

LANDAU, Hannibal, Mo.

LEUKEMIA IN INFANCY; FIVE CASES. OTTO SAXL, Jahrb. f. Kinderh. **150**:228 (Nov.) 1937.

Reports of 5 cases of leukemia are given. All of these cases terminated as is usual with leukemia.

LANDAU, Hannibal, Mo.

Diseases of Lungs, Pleura and Mediastinum

SIGNIFICANCE AND PROGNOSIS OF SPONTANEOUS PNEUMOTHORAX DURING CHILDHOOD. H. WISSLER, Jahrb. f. Kinderh. **150**:11 (Sept.) 1937.

The results of treatment in 57 cases of spontaneous pneumothorax are discussed. In the majority the condition followed pneumonia. The entire mortality in this series was about two thirds. Abscesses were found in the majority of patients who came to autopsy.

Cases of encapsulated pneumothorax are discussed. There is considerable difficulty in differentiating this condition from pulmonary abscess, tuberculous cavities, postpneumonic pseudocavities and bronchiectatic cavities. As a whole the prognosis is not quite so unfavorable with this type.

LANDAU, Hannibal, Mo.

AUTOHEMOTHERAPY OF LOBAR PNEUMONIA. T. V. SIMON, Jahrb. f. Kinderh. **150**:157 (Oct.) 1937.

In his series of cases of lobar pneumonia treated by autohemotherapy the author was unable to find this method effective.

LANDAU, Hannibal, Mo.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

THE INFLUENCE OF THE TURNIP (BRASSICA RAPA) ON THE ACIDITY OF THE URINE AND THE STOOLS OF HEALTHY CHILDREN AND OF THOSE WITH DISORDERS OF THE GASTROINTESTINAL TRACT: A CONTRIBUTION TO THE USE OF RAW FOODS IN CHILDREN'S DIETS. V. LEPPO, Acta pædiat. (supp. 2) **27**:7, 1940.

A review of the literature reveals that raw vegetables and fruits enjoy growing popularity, not only in the diets of healthy children but as therapeutic agents in the treatment of diarrheal diseases. The banana and the apple have been most widely used. Since both of these fruits are difficult to get in Finland under normal circumstances and are virtually unprocurable in war time, a search has been conducted to find an indigenous substitute for them.

In this monograph of 98 pages are described the author's investigations on the native turnip (Brassica rapa), which has long been one of the most important native vegetables because of its extremely hardy character. The results are summarized as follows: The native turnip possesses nutritive properties similar to those of the banana and the apple. The somewhat low energy quotient of 290 calories per kilogram of weight which it provides is derived almost entirely from its carbohydrate content, for it contains almost no fat and little protein. The vegetable is rich in mineral salts; it contains 27.4 mg. of calcium per hundred grams, 387.1 mg. of potassium and 36.0 mg. of phosphorus. Its p_H is about 6.1. It contains cellulose and about 1.1 mg. of pectin per hundred grams. It is rich in ascorbic acid, containing 40 mg. per hundred grams; its antiscorbutic properties are fairly stable. Even small infants can eat enough of the vegetable to avoid scurvy. It also contains significant amounts of vitamin A.

Clinical experiments on 17 healthy children, aged 1 to 11 years, indicated that the native turnip can be eaten exclusively for several days without untoward effect. Such a diet leads to increased alkalinity of the urine; the stools become voluminous and spongy and smell strongly of turnips, and their p_H rises slightly. Favorable results were obtained with 13 children suffering from diarrhea. An extensive bibliography is appended.

McCUNE, New York.

Nervous Diseases

BIRDS AND MOSQUITOES AS HOSTS FOR VIRUS OF EASTERN EQUINE ENCEPHALOMYELITIS. W. A. DAVIS, Am. J. Hyg. (Sect. C) **32**:45 (Sept.) 1940.

Davis carried out an investigation to determine which mosquitoes native to Massachusetts are capable of transmitting eastern equine encephalomyelitis. Sixteen species of mosquitoes native to Massachusetts, including all the commoner members of the forty Culicinae known to the state, were obtained for study. In addition, Aedes aegypti was used as a control because it was already known to be a vector. The author also determined whether mosquitoes could become infected by feeding on wild birds, which may thus serve as a reservoir for the virus. He found that of the seventeen species of mosquitoes studied five (Aedes vexans, Aedes sollicitans, Aedes cantator, Aedes atropalpus and Aedes triseriatus) and a laboratory strain (A. aegypti) could transmit the virus of eastern equine encephalomyelitis from infected birds or mammals to other animals. No transmissions were obtained with the Culex, Mansonia and Anopheles genera of mosquitoes. Most mosquitoes of the genus Aedes probably can serve as vectors of the virus in the laboratory, but ecologic factors determine the importance of the different species in nature. If mosquitoes are the natural vectors of equine encephalomyelitis, A. vexans was probably the most important vector of the infection in the New England epidemic of 1938. Experimental evidence showed that birds (English sparrows, pigeons and cowbirds) could be infected with virus by the bite of infected mosquitoes and that such birds may serve as a source from which mosquitoes become infected. The results do not prove that birds are the natural reservoir of equine encephalomyelitis,

but it is likely that mosquitoes which become infected with virus from such birds in turn infect human beings and horses, birds or other animals.

J. A. M. A.

VITAMIN C IN EPILEPSY: DILANTIN SODIUM NOT A CAUSE OF VITAMIN C DEFICIENCY. H. HOUSTON MERRITT and ALTHEA FOSTER, Am. J. M. Sc. **200**:541 (Oct.) 1940.

Swelling of the gums, in the form of benign hyperplasia, is a side effect of the administration of dilantin sodium to patients with epilepsy. A belief has been expressed that this was due to a deficiency of vitamin C induced by the drug. For a series of 257 ambulatory patients subject to convulsive seizures the authors found that the average vitamin C content of the plasma was 0.45 mg. per hundred cubic centimeters. The long-continued administration of dilantin sodium had no effect on the level of vitamin C in the plasma or on the absorption of vitamin C given by mouth. The low level of vitamin C was considered to be due to an inadequate diet and was readily corrected when an adequate diet and supplementary vitamin C were ingested. The hypertrophic gingivitis of such patients is not related to the vitamin C content of the plasma or to the utilization of vitamin C.

HENSKE, Omaha.

INFLUENZAL MENINGITIS TREATED WITH SULFAPYRIDINE. J. H. ARNETT, G. D. SHOUP and N. W. HENRY, Am. J. M. Sc. **200**:674 (Nov.) 1940.

Arnett, Shoup and Henry report the case of a white girl aged 13 who had been deaf since she recovered from an attack of cerebrospinal meningitis, at the age of 7 years. Influenzal meningitis developed, and Pfeiffer's bacillus was recovered. Four hours after admission she was given 2 Gm. (30 grains) each of sulfapyridine and sodium bicarbonate and thereafter 1 Gm. of each of these drugs every four hours night and day. The patient recovered from the meningitis. Ten days after admission to the hospital examination of the abdomen revealed moderate hydronephrosis of the right kidney. There was bilateral ureteral obstruction, which is a well recognized complication of sulfapyridine therapy. The report emphasizes (1) the value of sulfapyridine in the treatment of influenzal meningitis, (2) its potentialities for damage to the upper portion of the urinary tract and (3) satisfactory recovery after complete ureteral blockage.

MICHAELS, Boston. [ARCH. NEUROL. & PSYCHIAT.]

ISOLATION OF HERPES SIMPLEX AND DEMONSTRATION OF INTRANUCLEAR LESIONS IN A CASE OF ACUTE ENCEPHALITIS. M. A. SMITH, E. H. LENNETTE and H. R. REAMES, Am. J. Path. **17**:55 (Jan.) 1941.

A 4 week old infant was admitted on the fourth day of an illness characterized by the onset of irritability, refusal to nurse and twitchings on the left side of the body. The patient died after five days of progressive cerebral symptoms without appreciable elevation of temperature. No organisms were grown either from the spinal fluid during life or from brain tissue taken at autopsy.

Sections of the medulla, the pons and the cerebellum showed, in addition to signs of meningoencephalitis, the unusual feature of intranuclear inclusion bodies resembling those seen in herpetic lesions. Moreover, these bodies were reproducd in two species of animals by intracerebral inoculation of a virus isolated from the brain tissue and identified by immunization tests as that of herpes simplex.

The authors after a review of the literature state that they regard this as the first reported case of acute encephalitis due to herpes simplex virus in which the "etiological significance of the virus has been established by the demonstration of typical herpetic inclusion bodies in human brain tissue." THOMAS, Chicago.

THE GREATER RESISTANCE OF VERY YOUNG ANIMALS TO ARREST OF THE BRAIN CIRCULATION. HERMAN KABAT, Am. J. Physiol. **130**:588 (Sept.) 1940.

The young dog is much more resistant to acute asphyxia than is the adult animal. The brain of the young animal is much more resistant to arrest of its circulation than is the adult organ. This has been demonstrated by quantitative studies of survival time, recovery time and revival time after temporary complete arrest of the cephalic circulation. The respiratory center in the newborn dog apparently will continue to function seventeen times as long as that in the adult dog after complete arrest of the flow of the blood in the brain. The ability of the newborn dog to achieve complete functional recovery after periods of complete arrest of the circulation in the brain is approximately 400 per cent greater than that of the adult animal. The change with age in the resistance of the brain to arrest of the circulation follows a hyperbolic curve, decreasing rapidly in the first month and more gradually later. The resistance is diminished to the adult level at the age of 4 months. Spinal shock does not supervene during arrest of the circulation in the brain in young dogs. The relation of the increased resistance to anoxia of the brain in the young animal to changes with age in metabolism and in the vascularity of the brain is discussed.

In discussing the brain of the newborn human infant, the author points out that while considerable clinical evidence supports the conclusion that the brain tissue of an infant can sustain much less oxygen deprivation than can the adult organ, clinical observations on patients with asphyxia neonatorum have revealed that the newborn infant can recover completely after a period of severe asphyxia prolonged far beyond what would constitute fatal asphyxia for the adult. The author has come to the conclusion, therefore, that there is good reason to believe that the brain of the human infant is more resistent to anoxia than the adult organ.

NOURSE, Cleveland.

MENINGEAL BLOOD VESSELS IN TUBERCULOUS MENINGITIS. N. W. WINKELMAN and MATTHEW T. MOORE, Am. Rev. Tuberc. **42**:315 (Sept.) 1940.

The blood vessels of the meninges in the midst of a tuberculous exudate undergo changes both inflammatory and proliferative, which are due, in all probability, both to mechanical and to toxic factors. In type they range from a pure, acute inflammatory process to a chronic proliferative phase, with the inflammatory picture still present mainly in the adventitia and, to a lesser extent, in the intima and media. In the adventitia the lesions are in reality an extension of the tuberculous process from the subarachnoid space, and they partake of the pathologic changes in the surrounding tissues. The media seems to play a passive part. The changes in this structure are largely determined by the degree of adventitial involvement externally and the type of intimal involvement internally. The intimal changes vary from simple subendothelial inflammatory infiltration to proliferation and infiltration and closure of the vascular lumen. There is, however, no single unit change which is pathognomonic of tuberculosis, except the occurrence of an actual tubercle within the vessel wall. Only the collective changes permit of a diagnosis of tuberculous arteritis.

EUGENE H. SMITH, Ogden, Utah.

SIGNIFICANCE OF APHASIA AS A SYMPTOM OF OTOGENIC EXTRADURAL ABSCESS. FRANZ ALTMANN, Arch. Otolaryng. **31**:819 (May) 1940.

Aphasia as a symptom of otogenic extradural abscess is rare; it is caused in some instances simply by the external pressure of the abscess. Two illustrative cases are presented. Generally, the main factor in the development of aphasia is inflammatory involvement of the leptomeninges and the superficial layers of the brain associated with collateral edema. The diagnosis can be established with a degree of certainty only in cases in which there is a predominance of external pressure. If inflammatory changes are paramount, differential diagnosis is virtually impossible.

GREENWOOD, Chicago.

ENCEPHALITIS PERIAXIALIS DIFFUSA OF SCHILDER. DAVID L. REEVES and LUCILE R. ANDERSON, Arch. Pediat. **57**:620 (Oct.) 1940.

The authors report the case of a 10 year old Mexican girl who had encephalitis periaxialis. Epileptiform attacks were the conspicuous initial symptoms. Of interest was the observation at the postmortem examination of a subdural hematoma on the right side, which was not demonstrable in the encephalograms.

The clinical and pathologic manifestations are discussed briefly. The authors contend that the disease occurs more frequently than is evidenced by the reports in the literature.

ORR, Buffalo.

PNEUMOCOCCIC TYPE XIX MENINGITIS WITH RECOVERY. HARRY LEICHENGER and S. H. ABELSON, Arch. Pediat. **57**:775 (Dec.) 1940.

The case of a 7 year old boy with meningitis due to type XIX pneumococci is reported. Recovery followed the combined use of antipneumococcus serum and approximately 1,000 grains (64.8 Gm.) of sulfapyridine (2-[paraaminobenzenesulfonamido] pyridine) and its sodium salt.

ORR, Buffalo.

AGENESIS OF THE CORPUS CALLOSUM ASSOCIATED WITH PORENCEPHALY. E. HAROLD SHYROCK, JAMES F. BARNARD and ROBERT S. KNIGHTON, Bull. Los Angeles Neurol. Soc. **5**:146 (Sept.) 1940.

In the case described by Shyrock, Barnard and Knighton, the multiparous mother of the patient exhibited transient vaginal bleeding at the eighth month of pregnancy but delivered an apparently normal male infant at full term. The child had bronchopneumonia when 6 weeks old. Extensor spasms and a rash over the face and neck appeared when he was 3 months old, and persisted. He never sat up. Neurologic examination at 9 months of age revealed that the child was mentally retarded, unresponsive and apparently blind; the pupils reacted to light. There was no paralysis, but the knee jerks were hyperactive. The head was normal in size and the neck retracted. The leukocyte count was 24,950; the Kahn and Kline reactions were negative, as had been the mother's during pregnancy. The child died, at the age of 9 months, with a carbuncle on the neck and an abscess of the lung.

Autopsy revealed a large porencephalic cavity in each frontoparietal area, with complete absence of the corpus callosum, septum pellucidum and hippocampal commissure. Thus, a large opening extended through the cerebrum from one side to the other. The roof of the third ventricle was missing, and this cavity communicated with a midline arachnoid cyst. Microgyria was present around the margins of the porencephalic openings; the sulci on the medial surfaces of the hemispheres were radially disposed; the parieto-occipital and calcarine sulci were separated on the right side; the optic nerves were small; aberrant masses of cortical tissue were observed beneath the ependyma over the basal ganglia, and the subcortical white matter was greatly reduced in amount. Along the dorsal margin of the porencephalic cavity of the right hemisphere was a sickle-shaped fasciculus the fibers of which had their origin in the parolfactory areas of both hemispheres and terminated in the hippocampal gray matter of the temporal lobes. Microscopically, there were no evidences of softening, but round cell infiltrations were seen, with proliferation of the meninges and ependyma. The pyramidal system seemed to be absent. The internal granular layer of the calcarine cortex was imperfectly laminated, and the ganglion cells of the lateral geniculate body were not arranged in laminas.

Shyrock, Barnard and Knighton emphasize the disparity between the extreme anatomic defects and the slight clinical manifestations. They believe the arrest of development occurred at about the fourth fetal month and may have been due to a chronic inflammatory process at that time. Apparently, it was not due to vascular lesions, syphilis, trauma at birth or any postnatal infection.

MACKAY, Chicago. [ARCH. NEUROL. & PSYCHIAT.]

CHRONIC PROGRESSIVE DEGENERATION OF THE SUPERIOR CEREBELLAR CORTEX (PARENCHYMATOUS CORTICAL CEREBELLAR ATROPHY). CYRIL B. COURVILLE and ARNOLD P. FRIEDMAN, Bull. Los Angeles Neurol. Soc. **5**:171 (Sept.) 1940.

Courville and Friedman report the case of a white woman who had had "spinal meningitis" when a baby, with inability to talk or walk thereafter until she was 12 years old. When 33 years of age she began to have choreiform movements and awkwardness of her hands, as well as an unsteady gait. During the next nine years she suffered from progressive ataxia and numerous falls. One year before her death from gastric carcinoma, at the age of 42, examination revealed slurred speech, uncertain gait, ataxia of all the extremities, a positive Romberg sign and a pendular knee jerk, but no nystagmus. At autopsy the essential neurologic lesion observed was diffuse, irregular atrophy of the folia of the superior surface of the cerebellum, with some generalized reduction in the size of the hemispheres. Microscopically, the Purkinje cells were nearly all absent in the involved areas, and the glandular layer was reduced in cell content. The basket cells were well preserved. Most of the myelin was absent in the affected folia but was normal elsewhere. There was no gliosis, but the leptomeninges were adherent to the cortex, particularly in the secondary sulci, which were occasionally obliterated. Superficially the meninges were thickened and vascularized. No infiltrations were present. The olives, dentate nuclei and cerebellar peduncles were grossly normal.

Courville and Friedman reject most of the theories proposed in explanation of this condition. They think that it is not a disease entity but that it is due rather to a combination of diverse factors which lead to anoxia, involving particularly the superior surface of the cerebellum, which is pressed against the tentorium. The Purkinje cells, being most sensitive to deprivation of oxygen, are first to be damaged and the cells of the granular layer next.

MACKAY, Chicago. [ARCH. NEUROL. & PSYCHIAT.]

CONGENITAL DEFECTS OF THE CRANIAL NERVES: AN ASSOCIATED PORENCEPHALY AND AGENESIS OF THE CORPUS CALLOSUM DIAGNOSED BY VENTRICULOGRAPHY. D. L. REEVES, Bull. Los Angeles Neurol. Soc. **5**:184 (Dec.) 1940.

In the first case reported by Reeves, a girl aged 2 months, with a history of holding the breath, choking spells, cyanosis and hoarseness since birth, was found to have an elongated, edematous epiglottis, which caused laryngeal obstruction, pallor of both optic disks, ptosis of the right eyelid and a tendency for the right eye, but not the left, to close on crying ("jaw winking"). The child died of bronchopneumonia six weeks later; at autopsy examination of the brain was not permitted. In the second case a girl aged 6 months had had convulsions since the age of 2 months. Birth had been apparently normal. The child had never held up the head or sat alone. The head was acrobrachycephalic. There were a congenital coloboma of the left optic nerve and pigmentary degeneration of the retina. The pupils reacted sluggishly; the abdominal reflexes were absent, and a Babinski reaction was present on both sides. Lumbar puncture with the patient under medication showed a pressure of 375 mm. of spinal fluid. A ventriculogram revealed a large cavity in the midline connected with the lateral ventricles, the anterior horns of which were widely separated. The diagnosis was porencephaly with agenesis of the corpus callosum. If this diagnosis is subsequently verified this case will represent the earliest age at which agenesis of the corpus callosum has yet been diagnosed ventriculographically.

MACKAY, Chicago. [ARCH. NEUROL. & PSYCHIAT.]

THERAPY BY ELECTRICALLY-INDUCED CONVULSIONS. W. GREY WALTER, Brit. J. Phys. Med. **3**:146 (Aug.) 1940.

The author describes his apparatus and his technic for the production of convulsions with electricity.

He expresses the belief that the treatment might be of some benefit in dementia praecox, depression and melancholia and that it might be another approach to the problem of epilepsy.

HARTMAN, Cleveland.

DOUBLE INFECTION OF THE MENINGES WITH MENINGOCOCCUS AND GAERTNER'S BACILLUS. K. J. GUTHERIE and T. ANDERSON, Brit. M. J. **1**:193 (Feb. 8) 1941.

This is a report of a case of double infection of the meninges, as the title indicates. The primary infection, from which the child recovered, was meningococcic. The secondary infection, which was due to Gärtner's bacillus, or Bacterium enteritidis, caused the child's death.

ROYSTER, University, Va.

MARMORIC STATE OF THE CORPUS STRIATUM. A. BROGES FORTES, Arch. de pediat. d. Uruguay **12**:381 (June) 1940.

The author describes this malady as a congenital disease of extrapyramidal localization, in which there are symptoms of generalized muscular hypertonia, epilepsy and mental retardation. A thorough study of the etiology, pathogenesis, pathology, diagnosis and treatment is made. The author reaches the conclusion that in most cases the disease is fatal, there being no known treatment at present. The paper is illustrated with photomicrographs.

MASS OCCURRENCE OF MENINGOENCEPHALITIS IN AUTUMN OF 1935 AND SPRING OF 1936. LASZLO VON KULIN, Jahrb. f. Kinderh. **149**:183 (June) 1937.

The author reviews the numerous cases he observed in the fall of 1935 and the spring of 1936. Typical meningeal signs were present. The course was relatively short. Despite the similarity of the spinal fluid picture to that of poliomyelitis, he takes issue with those who classify this condition as an atypical form of poliomyelitis.

LANDAU, Hannibal, Mo.

APPEARANCE OF DOMINANCE AND DEGREES OF STIMULATION OF THE SUCKING CENTER. ALBRECHT PEIPER, Jahrb. f. Kinderh. **149**:201 (July) 1937.

The author states that there are two distinct phases in the act of sucking. These are designated as the regular and the periodic sucking movements.

Kymographic records purporting to illustrate this are reproduced.

LANDAU, Hannibal, Mo.

SO-CALLED ACETONEMIC CONVULSIONS AND KETOGENIC DIET IN THERAPY OF EPILEPSY. G. FANCONI, Jahrb. f. Kinderh. **149**:301 (Aug.) 1937.

Case histories of children with so-called acetonemic convulsions are given. The chief common characteristic is a high grade labile condition of the carbohydrate metabolism. The convulsive state is often precipitated by mild infections. It may occur but once in some; in other children this tendency is much more marked.

Fanconi also discusses his results with administration of the ketogenic diet to 6 children with epilepsy. One child was apparently cured; 2 were free from convulsions as long as they remained on the diet; 2 were uninfluenced, and he felt that 1 was made worse.

LANDAU, Hannibal, Mo.

Psychology and Psychiatry

PSYCHOMETRIC PERFORMANCE OF CHILDREN RECEIVING AMPHETAMINE (BENZEDRINE) SULFATE. CHARLES BRADLEY and EMILY GREEN, Am. J. Psychiat. **97**:388 (Sept.) 1940.

Although amphetamine sulfate is essentially a sympathicomimetic drug, it has been recommended as a stimulant to intellectual function. The drug, in 10 to

20 mg. doses, was given to 14 boys and 7 girls, all residents of the Emma Pendleton Bradley Home. These children were 9 to 13 years old. They had a wide variety of neuropsychiatric complaints, and all but 8 had a "normal" intelligence quotient, as judged by the Stanford-Binet scale.

Generally, no striking change in the intelligence quotient followed the use of amphetamine sulfate, but the intelligence quotients of 3 boys and 3 girls showed a change of ten or more points. Twelve patients who showed improvement in school performance had an average drop of four tenths of a point in their intelligence quotients. Fifteen children showed no significant effect of the treatment.

JAHR, Omaha.

PSYCHIATRIC ASPECTS OF PORENCEPHALY. E. L. BERNSTEIN, Am. J. Psychiat. **96**:723, 1939.

Bernstein describes 7 cases of porencephaly among approximately 1,000 patients in a psychiatric clinic. Heredity was poor in 5 cases. Inability to adjust socially was the most striking feature, followed by mental retardation. The patients were sluggish, plodding, dependent, inadequate, seclusive, resentful and defensive. They were superficial and irritable, and variations in mood were outstanding. Bernstein believes that the psychiatric picture did not differ greatly from that usually seen in epileptic patients. When the lesion was in the frontal lobes, as occurred in 2 cases, the patients were more definitely antisocial.

FORSTER, Boston. [ARCH. NEUROL. & PSYCHIAT.]

THE FUNCTION OF THE PSYCHIATRIC RESIDENTIAL SCHOOL. EARL SAXE, Bull. Menninger Clin. **4**:163 (Nov.) 1940.

The neurotic child becomes a problem child when he finds himself at odds with his environment. The pressures directed at him in an attempt to reform him more often than not aggravate his condition. As a rule, those who make up his environment understand him as little as he understands them. The psychiatric residential school offers relief from the surroundings which contributed to his maladaptation. It offers a scientifically controlled environment and a well trained staff to carry on an individual therapeutic program. This program tends to encourage the child in the acquisition of technics and skills which develop self confidence and the sense of security which accompanies achievement. Such accomplishments are of inestimable value both for recreation and for better social adjustment.

JAHR, Omaha.

PSYCHOANALYSIS OF CHILDREN. MARY O'NEIL HAWKINS, Bull. Menninger Clin. **4**:181 (Nov.) 1940.

The aims and the technic of psychoanalysis are discussed. Psychoanalytic therapy depends for success on its ability to uncover the unconscious drives and mechanisms which control human conduct. In cases of deep-seated neuroses of childhood, in which there are distortion of personality and consequent maladjustment, this type of therapy often serves not only as a cure of the immediate symptoms but, what is of tremendous importance, it may act as a prophylactic against future problems relating to character deviation.

JAHR, Omaha.

THE FACTOR OF HEREDITY IN PSYCHOPATHIC INFANTS. RICARDO OLEA G., Arch. d. Hosp. niños Roberto del Rio **9**:185 (Oct.) 1940.

This factor is discussed and illustrated by case histories.

SANFORD, Chicago.

NEUROPATHY OF THE INFANT. PEDRO RUEDA, Arch. de pediat. **12**:13 (Sept.) 1940.

The author defines as a neuropathic child one with "congenital nervous irritability resulting in distressing singular or multiple manifestations, which do not endanger life, disappear toward the end of the first part of infancy and leave, as a sign of their passage, a superior intelligence which lasts till adult life." After a careful differentiation is made between spasmophilia and neuropathy as previously defined, symptoms of this disease are summarized as follows: intellectual precocity, neuromuscular hypertonia, vascular irritability and digestive disorders, which, the author points out, are the most important, for they may mislead the pediatrician as they resemble closely toxoinfective and digestive disorders.

As probable causes, specific heredity, alcoholism among ancestors, nervous parents and parathyroid disturbances are mentioned. The author strongly favors the last-mentioned factor and advises the use of parathyroid extracts for treatment, except in cases in which there are serologic findings indicative of syphilis and antisyphilitic treatment is indicated. Professor Rueda reports 13 cases in which subcutaneously administered parathyroid extract (20 dog units per cubic centimeter) was used when syphilis was not present and the arsenobenzenes when it was. All of the patients were cured.

SOTO, Habana, Cuba.

NEW FORM OF ACUTE DEMENTIA IN CHILDHOOD. J. KÖNIG and I. ZIMÁNYI, Ann. pædiat. **155**:305 (Sept.) 1940.

The patients, who were children with a new form of acute dementia, developed normally for a certain time before the occurrence of the first symptoms, which were motor symptoms similar to those of genuine epilepsy but which did not improve with antiepileptic treatment. After six months to a year at the latest, there were associated serious psychic disturbances, which progressed to dementia in a short time (two months to a year). During this time, the motor functions and the reflexes remained intact. Before the onset of the disease the idiotic child seemed to be intelligent, and neurologic symptoms did not develop for a long time. In a late stage following the development of dementia, there occurred ataxic symptoms indicating involvement of the frontal lobe.

The encephalogram was characteristic.

In 1 case puncture revealed atrophy of the frontal cortex. In the other case only the cells of the third layer showed abnormalities. No inflammatory reactions or signs of destruction of the white substance of the brain were detected. By the lack of neurologic symptoms referable to an organic lesion, the disease described may be differentiated from the well known diseases associated with idiocy and convulsions. By the encephalographic findings and the histologic picture it is differentiated from the other diseases in which there are no neurologic signs due to an organic lesion but in which idiocy and convulsions are present (dementia praecox and genuine epilepsy).

AUTHORS' SUMMARY.

Diseases of the Genitourinary Tract

UNUSUAL CYSTIC CHANGE IN BOTH OVARIES OF A 16 YEAR OLD GIRL. C. FAHRIG, Beitr. z. path. Anat. u. z. allg. Path. **103**:248, 1940.

Both ovaries weighed about 650 Gm. and were oval and flattened, measuring 18.0 cm. in length, 12.0 cm. in breadth and 6.5 cm. in thickness. They contained innumerable follicular cysts, ranging in size up to that of a cherry; the cysts were filled with clear, watery fluid and were separated from each other either by the cyst walls or by edematous, swollen septums. The cysts were lined by one or more layers of epithelial cells bounded by a thecal intima. There was no evidence of luteinization. Death resulted from lymphatic leukemia a little more than a year after operation. At autopsy there were no abnormal changes in the uterus and tubes; the endometrium was smooth, pale and of normal thickness; the anterior

lobe of the hypophysis was not enlarged but showed a marked increase in cells containing eosinophilic granules. On morphologic grounds and because an anterior pituitary extract containing the gonadotropic factor induced in immature female mice cystic change of the ovaries essentially similar to that observed in his patient, the author reaches the conclusion that excessive production and hyperactivity of the anterior pituitary follicle-stimulating hormone is responsible for multiple follicular cysts of the human ovary. R. J. LEBOWICH. [ARCH. PATH.]

PERINEPHRITIC ABSCESS IN INFANCY. H. RIEGER, Jahrb. f. Kinderh. **149**:178 (June) 1937.

Two cases of perinephritic abscess are presented, both of which ended fatally. The rarity of this condition in infancy is discussed.

The difficulty of diagnosis is stressed. Early diagnosis is essential if the outcome is to be successful.

The characteristic features in the adult, consisting of a palpable mass, positive urinary findings and roentgen signs, are seldom present. Rupture of the abscess into the peritoneal cavity is one of the worst complications and almost always ends in the death of the child. LANDAU, Hannibal, Mo.

RENAL COMPLICATIONS FOLLOWING TREATMENT WITH SULFAPYRIDINE. HERBERT LEBEL, ERLING SCHROEDER and MARGRETHE SIMESEN, Acta med. Scandinav. **105**:395, 1940.

A survey of the literature on renal complications during treatment with the drug is given. Analysis showed that concrements from the renal tubules or pelves or from the ureters consisted practically entirely of the acetylated compound. The authors studied the solubility of the drug and of its acetylated derivative in distilled water and in urine of varying p_H. The solubility was little increased when the p_H increased from 4.0 to 7.0, but it was considerably increased if the reaction became alkaline. The urine of patients receiving the drug was analyzed and was found to be 3 to 5 times oversaturated, and on standing, even at 37 C. (98.6 F.), precipitation occurred. The explanation offered for the fact that urinary complications are not more frequent is the great stability of urine which is oversaturated with the drug. Although the acetylated compound is only slightly less soluble, the stability of its oversaturated solution is much less than that of the oversaturated solution of the free drug. The authors report a case in which complete anuria of three days' duration was relieved by catheterization of the ureters and washing out of the renal pelves. Although the concentration of urea in the blood rose to 152 mg. per hundred cubic centimeters seven days after the treatment, renal function and the urine were normal. KAJDI, Baltimore.

Diseases of the Ductless Glands; Endocrinology

I. AN EXPERIMENTAL STUDY OF THE EFFECT OF THE PITUITARY ON THE MOTILITY OF THE GASTRO-INTESTINAL TRACT: A PRELIMINARY REPORT. SAMUEL MORRISON and MAURICE FELDMAN, Am. J. Digest. Dis. **7**:451 (Nov.) 1940.

This experimental work was done on dogs (average weight 8 Kg.). The administration of extract of the anterior lobe of the pituitary produced no demonstrable effect on the motility of the gastrointestinal tract of normal dogs or of dogs which had been subjected to (a) vagotomy and hypophysectomy, (b) vagotomy, thyroidectomy and hypophysectomy or (c) thyroidectomy and hypophysectomy.

Thyroidectomy and hypophysectomy did not affect the motility of the gastrointestinal tract. Normal secretory values were obtained with gastric test meals for the dogs which had been operated on but were otherwise untreated.

MORRISON, Savannah, Ga.

II. An Experimental Study of the Effects of the Pituitary and Thyroid Glands on Carbohydrate Metabolism: A Preliminary Report. Samuel Morrison and Maurice Feldman, Am. J. Digest. Dis. **7**:453 (Nov.) 1940.

This experimental work was done on dogs (average weight, 8 Kg.). The administration of extract of the anterior lobe of the pituitary to normal dogs had a hyperglycemic, or diabetogenic, effect. Dextrose tolerance tests on 2 dogs subjected to hypophysectomy and vagotomy, of which 1 had and 1 had not undergone thyroidectomy, revealed an increased tolerance and increased mobilization, with a hypoglycemic tendency. The blood sugar curves of hypophysectomized dogs subjected to vagotomy, thyroidectomy or both approached normal when extract of the anterior lobe of the pituitary was administered. The administration of thyroid to normal dogs produced hyperglycemia, while its administration to dogs subjected to hypophysectomy with and without thyroidectomy resulted in blood sugar curves which were normal.

Morrison, Savannah, Ga.

Involution of the Thymus of the Young Albino Rat Under Treatment with Testosterone Propionate. Edward C. Persate Jr., Am. J. Physiol. **130**:384 (Aug.) 1940.

The thymus of male and female albino rats under 100 days of age was caused to involute by giving injections of testosterone propionate.

Nourse, Cleveland.

The Prolonged Action of Acidified Solution of Protamine Zinc Insulin. Melville Sahyun, Am. J. Physiol. **130**:521 (Sept.) 1940.

A method is described for the preparation of a clear, acidified solution of protamine zinc insulin containing 5 mg. of protamine and 0.2 mg. of zinc per hundred units. Its subcutaneous injection into fasting rabbits causes prolonged hypoglycemia which is more pronounced than that which follows the injection of a similar amount of crystalline insulin with or without added zinc.

Nourse, Cleveland.

A Syndrome of Polydipsia and Polyuria Induced in Normal Animals by Desoxycorticosterone Acetate. Charla Ragan, Joseph W. Ferrabee, P. Phyfe, Dana W. Atchley and Robert F. Loch, Am. J. Physiol. **131**:73 (Nov.) 1940.

Large doses of desoxycorticosterone acetate induce in normal animals (dogs) a syndrome of polydipsia and polyuria similar to that of diabetes insipidus. The syndrome differs from diabetes insipidus in at least two important respects: administration of pitressin has relatively little effect and restriction of fluids does not cause dehydration.

Nourse, Cleveland.

The Effect of Thyroidectomy on Serum Cholesterol and Metabolic Rate in the Rabbit. Walter Fleischman, Harris B. Schumacker Jr. and Lawson Wilkins, Am. J. Physiol. **131**:317 (Dec.) 1940.

Thyroidectomy in the rabbit is followed by a sharp rise in the serum cholesterol to an average of 171 per cent above the preoperative level. After the first rise the level of serum cholesterol fluctuates markedly and finally becomes stabilized after about twelve weeks at a point which on the average is 80 per cent above the base level. The basal metabolic rate decreases gradually in six weeks to about 40 per cent below the preoperative level.

Nourse, Cleveland.

THE RELATIONSHIP BETWEEN SALT INTAKE AND THE POLYURIA OF EXPERIMENTAL DIABETES INSIPIDUS. CHARLES A. WINTER, D. G. SATTLER and W. R. INGRAM, Am. J. Physiol. **131**:363 (Dec.) 1940.

Diabetes insipidus was produced in cats by interruption of the supraoptico-hypophysial tracts. Cats with diabetes insipidus thus induced show a close parallelism between the salt intake and the urinary volume when the ingestion of sodium chloride is abnormally high, but this parallelism does not hold when the salt intake is normal or below normal. During fasting the urinary volume of a cat with diabetes insipidus falls almost to the level which is characteristic of a normal animal. The disappearance of polyuria is not due, however, to the deprivation of salt which accompanies fasting, because if the salt intake is kept at a normal level during the fast by adding salt to the drinking water, the urinary volume falls just the same. Furthermore, the animal continues to have polyuria of practically the same degree when placed on a diet almost completely free of salt.

NOURSE, Cleveland.

THE TREATMENT OF DIABETES MELLITUS WITH A FOUR-MEAL DIET: A MEANS OF CIRCUMVENTING CERTAIN DIFFICULTIES ARISING IN THE USE OF PROTAMINE ZINC INSULIN. H. M. MARGOLIS and V. W. EISENSTEIN, Ann. Int. Med. **14**:667 (Oct.) 1940.

The authors report their experience with a four meal diet with patients whose diabetes was controlled with protamine zinc insulin. The meals were divided as follows: one fifth of the total caloric intake at 8:00 a. m., one fifth at noon, two fifths at 5 p. m. and one fifth at 9:30 p. m. The authors express the belief that with this dietary regimen more adequate control of the diabetes was obtained, more quickly than before and with less danger of hypoglycemic shock.

GARD, Galveston, Texas.

HYPERTROPHY OF THE THYMUS IN VERNAL CONJUNCTIVITIS. GUSTAVO ALAMILLA, Arch. Ophth. **23**:1231 (June) 1940.

Vernal conjunctivitis occurs in children and in the spring; its incidence diminishes during cold weather. The etiology is unknown, but it has been assumed that the disorder has an allergic basis, although some unusual results have been obtained with the use of various endocrine preparations. In the case of a 6 year old boy who had well defined vernal conjunctivitis, the author noted a cessation of all symptoms while the child was independently undergoing irradiation of his extremely hypertrophic thymus.

WESCOTT, Chicago.

VARYING MANIFESTATIONS OF THYROID GLAND DYSFUNCTION IN INFANTS, CHILDREN AND ADOLESCENTS. CHARLES GILMORE KERLEY, Arch. Pediat. **57**:694 (Nov.) 1940.

Nine cases of cretinism in which treatment with desiccated thyroid was used are reported. Excellent results were obtained in each instance. Kerley emphasizes the point that the potency of desiccated thyroid decreases with age and exposure and that to obtain prompt and satisfactory effects the fresh product should be used. The maximum dosage will be required for patients between 8 and 14 years of age who have pronounced hypothyroidism.

ORR, Buffalo.

SIMMONDS' SYNDROME. ERIK MOGENSEN, Acta med. Scandinav. **105**:360, 1940.

A review of the history, pathologic characteristics, etiology, symptoms and diagnosis of this syndrome is given. Emphasis is placed on the fact that cachexia is a late development and that its absence is therefore not contradictory to the diagnosis. The differential diagnosis from anorexia nervosa is discussed in par-

ticular detail. In the author's personal experience, the most efficient therapeutic measure has been the administration of chorionic gonadotropin.

KAJDI, Baltimore.

ADRENAL HYPERTROPHY IN INFANTS: A NEW CLINICAL ENTITY OF THE NEONATAL PERIOD. R. DIJKHUIZEN and E. BEHR, Acta pædiat. **27**:279, 1940.

This interesting and significant contribution to the nosology of the neonatal period is based on 4 cases; 2 were observed by the authors; notes on the third were contributed by Schippers and De Lange and on the fourth by Gorter and Lignac. The outstanding clinical symptom of the syndrome consisted of regurgitation, commencing a few days after birth and culminating in vomiting, diarrhea and dehydration between the fourteenth and the twenty-first day of life. In all 4 cases an erroneous diagnosis of partial intestinal obstruction was made, and 1 patient was operated on. Despite modern supportive treatment 2 of the infants died within forty-eight hours after the onset of violent vomiting; 1 survived a few weeks and 1 two months. Necropsy in 3 cases revealed as virtually the only pathologic change massive enlargement of the adrenal glands, which weighed 22, 24 and 34 Gm. Grossly, the surface of the glands had a corrugated, cerebriform appearance. The microscopic pattern lacked uniformity. In 1 case the cellular pattern was distinctly peculiar; in the second it was less unusual and in the third quite normal. Attention is drawn to the fact that 3 of the patients were boys. Two were brothers, 1 of whom exhibited rudimentary pseudohermaphroditism in the form of perineal hypospadias.

The literature contains fragmentary allusions to similar cases. Hammer mentioned a 6 week old boy who died of an obscure illness and whose adrenals together weighed 15 Gm. Dietrich and Siegmund and Broster and Vines commented on the enlargement of the adrenals of 2 infants who died of intestinal disorders. Pagel, Rössle and Marchand have each recorded cases of congenital adrenal hypertrophy. Marchand's patient also had some features of pseudohermaphroditism. The extensive literature on the adrenogenital syndrome contains little that is relevant to the present topic. The suggestion is submitted that the clinical symptoms arise from excessive production of one of the cortical hormones.

MCCUNE, New York.

Diseases of the Muscles, Bones, Joints and Lymph Glands

THE ANTIQUITY OF ACHONDROPLASIA. ADRIEN BLEYER, Ann. M. Hist. **2**:306, 1940.

Achondroplasia is one of the oldest known pathologic conditions. A humerus showing signs of this condition was found in the tomb of King Zer, of the first Egyptian dynasty. The discovery by Guy Brunton of an entire achondroplastic skeleton dating from the predynastic period carries the history of the disease still farther back. This skeleton is preserved in the Museum of the Royal College of Surgeons in England.

In historic Egypt representations of subjects with achondroplasia were frequent, as is shown by the many figures of the gods Ptah and Bes, both of whom showed clear signs of the condition.

The first good description of the disease in the medical literature was given by Sommering in 1791, and it was named by Parrot in 1878. However, it was Marie's fine description, which appeared in 1900, that made the medical world conscious of this condition.

ROSENTHAL, St. Paul.

THE RELATIONSHIP BETWEEN AMYOTONIA CONGENITA AND CONGENITAL MYOPATHY. J. W. ALDREN TURNER, Brain **63**:163, 1940.

Turner describes a family of 13 children, 6 of whom suffered from amytonia congenita. No other members of the family were affected.

The condition was present at birth, and probably before, as the mother could tell from the lack of fetal movements that the later children would prove to be affected. The picture was similar in all 6 patients. At birth, the infants had extreme hypotonia, and the limbs could be moved freely into abnormal postures. The muscles were flabby but not atrophied. Reflexes were absent. Voluntary movement was impossible. Strength gradually increased, reflexes appeared and hypotonia diminished, and by the age of 4 or 5 years the children could walk with a waddling gait.

The hypotonia diminished in adult life, and strength was sufficient to permit moderately strenuous pursuits. However, it was observed that at about the age of 6 localized wasting of the sternocleidomastoid, pectoral, trapezius and triceps muscles had developed in all the children, with slight atrophy of the serratus magnus, the spinati, the latissimus dorsi and the deltoid muscles. There was no localized atrophy of the legs, but 3 of the 4 patients who survived walked with a waddling gait. The atrophy was not progressive.

The transition of this condition from a state of amyotonia and marked flaccidity to one of myopathy with localized muscular atrophy marks the disease as a congenital myopathy. In further support of the myopathic basis of this form of amyotonia congenita is the fact that it is familial, that cases of amyotonia congenita and muscular dystrophy have been reported in the same family and that a few cases of muscular dystrophy appearing at birth have been observed.

Against this opinion are the facts that flaccidity is unusual in the myopathies and wasting rare in amyotonia. The transitional state in the cases described tends to negate this objection. A more serious objection is the fact that the myopathies are usually, but not always, progressive and that any return of the tendon reflexes, such as was observed in these cases of amyotonia, is rare.

Although no pathologic studies are reported, it is believed that the condition here described differs from that of amyotonia congenita, which is related to Werdnig-Hoffmann disease and in which the anterior horn cells are affected. Although the prognosis differs greatly, clinical differentiation of the two conditions is difficult. The conclusion must be reached that amyotonia congenita is a symptom rather than a disease and that it may be caused either by a congenital myopathy, as in the family reported on here, or by a spinal disorder bearing a close relation to Werdnig-Hoffmann disease.

MASLAND, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

SYNDROME ACCOMPANIED BY GENERALIZED TRUE OR SPURIOUS PLATYSPONDYLISIS. JULES R. DREYFUS, Jahrb. f. Kinderh. **150**:42 (Sept.) 1937.

The condition is generally found in children from 2 to 13 years of age. They complain of pain or weakness in the back and have lordosis or kyphosis. It is often seen immediately following an infectious disease. The principal roentgen findings are a generalized widening of the vertebral bodies and a diminution in height. The bony changes which accompany several of the other bone dyscrasias, such as achondroplasia and Morquio's disease, are lacking. Rest in bed and plaster casts are advised in the treatment of this condition. Corsets are also used.

LANDAU, Hannibal, Mo.

Diseases of the Eye

CONGENITAL PREPAPILLARY CYST CONTAINING A MOVING VASCULAR LOOP. J. M. LEVITT and R. I. LLOYD, Am. J. Ophth. **22**:760 (July) 1939.

The case of a 15 year old girl is reported. She was told by the school physician that there was something wrong with the left eye. Each eye had vision of 20/40. Under homatropine cycloplegia vision of 20/40 was improved to 20/20 with a —0.50 sphere. The media and fundus of the right eye were normal. The media of the left eye were clear. There was a grayish white circular elevation covering

part of the disk and extending beyond it at the lower inner margin. With the Gullstrand binocular ophthalmoscope this was found to be a cyst, and a loop was seen within, moving up and down behind the retinal blood vessels with every motion of the eye. The blindspot was moderately enlarged, and with red-free light the binocular scope showed the nerve fibers running across the front of the cyst. The peripheral field of the eye was about 10 degrees less than that of its fellow.

W. S. REESE. [ARCH. OPHTH.]

GYRATE ATROPHY OF THE RETINA AND CHOROID FOLLOWING RETINITIS PIGMENTOSA: REPORT OF TWO CASES. W. T. DAVIS and ERNEST SHEPPARD, Arch. Ophth. **23**:1252 (June) 1940.

The cases of 2 brothers whose parents were cousins are reported. A diagnosis of retinitis pigmentosa was made, and several years later typical gyrate atrophy of the retina was discovered.

WESCOTT, Chicago.

WHAT THE PEDIATRICIAN MIGHT DO TO SAVE SIGHT IN THE PRE-SCHOOL CHILD. PHILIP MOEN STIMSON, Arch. Pediat. **57**:269 (May) 1940.

A pediatrician in examining a child's eyes should not be content with simple visual tests. Heredity, diet and physical handicaps may be the underlying cause of eye strain. Early recognition of muscular imbalance may prevent permanent visual damage.

ORR, Buffalo.

MYCETOMA OF THE EYELID. J. S. ALDRIDGE and R. KIRK, Brit. J. Ophth. **24**:211 (May) 1940.

The patient was a Nubian girl aged approximately 4 years. A tumor had begun to develop in the upper eyelid at the outer angle of the right eye two months before and had attained the size of a marble. Sections of the tumor showed the morbid histologic appearance commonly associated with a fungous infection—a chronic nonspecific inflammatory lesion characterized by hyaline fibrosis and plasma cell and leukocytic infiltration, with occasional small imperfect giant cell formations. In the more densely infiltrated parts fungous grains could be seen irregularly distributed. Little in the way of detailed structure could be made out in the grains, and cultures were out of the question, but their appearance and relation to the associated histopathologic changes are sufficiently typical to establish a diagnosis of mycetoma. The authors could find but 2 other cases of such ocular involvement in the literature. In 1 of these cases the patient came from approximately the same region of northern Sudan as did the patient in the present case.

The article is accompanied with illustrations.

W. ZENTMAYER. [ARCH. OPHTH.]

MICROPHTHALMIA AND THE VISUAL PATHWAYS. A CASE ASSOCIATED WITH BLINDNESS AND IMBECILITY, AND SEX-LINKED. S. E. WHITNALL and R. M. NORMAN, Brit. J. Ophth. **24**:229 (May) 1940.

The authors give the following summary of the case reported in their article:

"(1) A microphthalmic imbecile 17 years of age, with a unique ophthalmological family history, presented at autopsy special features in his eyeballs and visual tract.

(2) The eyeballs were completely disorganized and could never have transmitted light—equivalent to an anophthalmic condition.

(3) The effects of this deprivation of light impulses were reflected in a pronounced poorness of development of the optic nerves, chiasma, tracts and lateral geniculate bodies.

But beyond this region:

(4) The superior quadrigeminal bodies were quite normal in size and structure.

(5) The optic radiation was well formed, and its fibres were myelinated.

(6) The cortical visual areas, though their surface extent was much less than usual and one was grossly deformed, presented a normal lamina granulosa and a well marked stria of Gennari.

(9) The imbecile condition is possibly explained by an imperfect general cortical cellular composition; for there were no gross cerebral pathological lesions present."

The article is illustrated. W. ZENTMAYER. [ARCH. OPHTH.]

RARE OCULAR DEVELOPMENTAL ANOMALIES IN ASSOCIATION WITH CONGENITAL AND ACQUIRED BLINDNESS: CLINICAL "PROOF" OF VITREOUS DEVELOPMENT. J. H. YOUNG, Brit. J. Ophth. **24**:597 (Dec.) 1940.

The patient was a man 21 years of age. He was totally blind. The right eye had become blind three years previously, after a severe attack of pain and inflammation. A tentative diagnosis of uveitis complicated by secondary glaucoma was made. The left eye was congenitally blind and exhibited the following conditions:

Primitive optic "disk" with absence of the nerve head, no lamina cribrosa and a narrow bore optic cup of great depth; complete absence of the normal retinal vascular system in the nondetached and detached portions of the retina and the optic cup and complete absence of neuronal development; partial achoroidia on the temporal side and a maldeveloped choroid on the nasal side, in association with pigment deposition of an unusual type; rudimentary gray ciliary body (gray color due to the absence of pigment epithelium, normally developed from the neural ectoderm); partial aniridia; luxatio lentis (probable ectopia vera), associated with abnormal physical shape and structure with an auxiliary blood supply; a perfect vitreous; no evidence of any remains of the primitive hyaloid vascular system (this negative evidence is valuable, since retinal circulation is an outgrowth from this primitive system of vessels).

The author gives a diagnostic summary showing the stage at which the various lesions develop and also an embryologic interpretation of the findings. He states that the absence of a ciliary body and a normal retinal circulation indicate that these structures took no part in the development of a perfect vitreous.

He assumed that the lens played but a passing role in the development of vitreous and that the only structure left to form the "secondary" vitreous is in the nonvascular lining of the optic cup, which, in view of its immaturity, must be due to the functioning of its primitive cells, acting by virtue of their inherent determination and their special nature.

A point of interest is the optical and physical perfection of the vitreous, which has been maintained in its augmented state despite the almost complete absence of vascular structures within the eye. Two possibilities suggest themselves.

1. The remnants of the choroid were sufficient to maintain the volume and physical structures of the vitreous at their maximum efficiency (all other vascular structures being absent).

2. The vitreous when fully determined in development requires no maintenance whatever and while hermetically sealed within the globe and not subject to pathologic interference retains its efficiency unimpaired.

The author accepts the second of these possibilities.

The article is illustrated. W. ZENTMAYER. [ARCH. OPHTH.]

CONGENITAL HORNER'S SYNDROME, NOT CAUSED BY PARALYSIS OF THE OCULAR SYMPATHETIC NERVE. E. M. MONDINI, Lattante **11**:105 (April) 1940.

An 18 month old boy had had marked enophthalmos, constant miosis, internal strabismus and slight lid drop of the left eye since birth. Both cocaine and atropine caused dilatation of both pupils, a trifle more of the right than of the left.

Mondoni interpreted the Horner syndrome as an expression of a hypogenesis of the ciliary center of the spinal cord and not as paralysis of the sympathetic nerve fibers to the eye. HIGGINS, Boston.

BIOLOGY OF THE MALIGNANT MELANOMA OF THE CHOROID. W. GILBERT, Arch. f. Ophth. **141**:547, 1940.

Because of the uncertainty with regard to the tissue elements from which so-called sarcoma of the choroid takes its origin, Gilbert recommends the noncommittal term malignant melanoma for this tumor (the term generally used in the United States). The division of the course of malignant melanoma into four stages (introduced by Knapp seventy years ago), namely, (1) the stage of silent intraocular growth, (2) the stage of intraocular inflammation or of glaucoma, (3) the stage of peribulbar growth and (4) the stage of metastases, should be abandoned for many obvious reasons. In many instances metastases occur during the first stage. Stage 3 may directly follow stage 1. Small peribulbar growths may easily be overlooked despite careful inspection of the wound immediately after the enucleation and despite careful pathologic examination of the enucleated eye. Metastases that have developed during stage 1 may remain dormant until the primary tumor is removed. "I, therefore, recommend a classification that is based upon the biologic reaction of the bearer of the eye containing the tumor. . . . By virtue of this reaction the body may be able to keep under control and to destroy disseminated tumor cells. . . . If the body loses this faculty of control the disseminated tumor cells turn into rapidly growing metastases." Gilbert thus distinguishes between a premetastatic stage and a stage of established metastases. The stage of established metastases can, as a rule, be recognized by clinical and roentgen examination. The diagnosis of stage 1 can at this time only be made tentatively and by exclusion. One advantage of this new classification over the old is that it conveys a more nearly correct (not too favorable or too unfavorable) idea with regard to the prognosis. P. C. KRONFELD. [ARCH. OPHTH.]

Skin Diseases; Allergy

SUPRARENAL GLAND AND LACTOSE IN THE TREATMENT OF MAJOR ALLERGIC DISORDERS IN CHILDHOOD: A CLINICAL EVALUATION. STEPHEN D. LOCKEY, Arch. Pediat. **57**:724 (Nov.) 1940.

A concentrate of the whole adrenal gland plus lactose by mouth was used in the treatment of 163 cases of the so-called major allergic disorders of childhood, with clinical improvement in 82 per cent of the cases.

In cases of bronchial asthma the concentrate of adrenal gland and lactose reduced the frequency of attacks. The attacks which did occur were milder than those in the control group.

This therapy also alleviated the symptoms of hay fever. ORR, Buffalo.

HISTAMINE IN ANAPHYLAXIS AND ALLERGY. LAURENCE FARMER, Bull. New York Acad. Med. **16**:618 (Oct.) 1940.

The rationale of histamine therapy in some allergic conditions is discussed. Of a total of 48 patients treated during 1938 and 1939, 21 showed good results, 12 fair and 15 had no benefit from the treatment.

In the treatment of hay fever the author admits that direct desensitization at present yields a higher incidence of relief. This is explained by the fact that the histamine dosage is as yet not fully established. Qualitative results, however, can be achieved with histamine in the treatment of hay fever which compare favorably with those achieved through specific desensitization. Histamine therapy, the author concludes, is destined to mark a further advance in the treatment of allergic diseases. JAHR, Omaha.

ACRODYNIA. G. POPOVICIU and O. POP, Ann. pædiat. **156**:25 (Oct.) 1940.

Acrodynia is extremely rare in Rumania, but it seems to have occurred more frequently in recent times. One case had been reported before the authors published the reports of their first 2 cases. After these observations 3 other cases were

reported. To these might be added 2 or 3 cases of an abortive form of the disease which were observed during the last few years by the authors but in which a definite diagnosis was not made. They report a third case in this paper. The first case in Rumania was observed in Bucharest in 1932. There occurred in former years fairly extensive epidemics of so-called *exanthème miliaire* (Stroe and co-workers), sometimes complicated with encephalitis, as well as a relatively severe epidemic of infantile paralysis. All the other cases have been observed lately (1 was observed in 1931 but was only recently brought to the attention of the authors) in the northwest part of the country, where only small epidemics and sporadic cases of infantile paralysis and encephalitis occurred.

In the authors' cases all the classic symptoms were present. In addition, there was slight hydrocephalus in 1 case, with the spinal fluid under increased pressure but without an increased cell count or chemical changes. The concentration of sugar in the spinal fluid, however, approached the upper limit of normal. After encephalographic examination and treatment by withdrawal and reinjection of the patient's spinal fluid sudden improvement occurred. The orthostatic test (Danielopolu-Carniol) with 0.9 mg. of atropine sulfate and the epinephrine test showed a great increase in the tonus of the sympathetic system. The level of phosphorus in the blood was lowered in this case (the patient was a child aged 1¾ years), and that of calcium was near the lower limit of normal; the blood sugar was increased, as was the blood pressure, and the heart rate was accelerated. In the second case (that of a child of 17 months) the level of phosphorus in the blood was higher than in the first case and that of calcium was near the upper limit of normal, while the blood sugar was relatively lower. The chemical data in the first case should perhaps be considered as indicative of rickets, which might also point to the rachitic pathogenesis of the concomitant hydrocephalus, although every other clinical sign of rickets was absent in this case, while in the case without hydrocephalus there were various if discrete, rachitic bony changes. In the third case (that of a 1 year old child) there were no rachitic changes in the bones and no hydrocephalus or changes in the spinal fluid; the level of calcium in the blood was at the upper limit of normal, and that of phosphorus was lowered; the blood sugar was raised, and there was greatly increased tonus of the sympathetic system, which was proved by the test of Danielopolu and Carniol. In the last case, in accordance with the milder clinical character of the disease, there was gradual improvement after encephalographic examination and treatment by withdrawal and reinjection of the patient's spinal fluid.

AUTHORS' SUMMARY.

A CASE OF PITYRIASIS VERSICOLOR OF THE FACE. S. OCHI, Acta dermat. **34**:4 (Aug.) 1939.

The author reports the case of an 11 year old girl in whom lesions developed on the forehead and cheeks due to Microsporon furfur. He quotes Iseki, who has observed numerous cases of pityriasis versicolor of the face in natives on the island of Palau in the South Seas. BLOOM, New York. [ARCH. DERMAT. & SYPH.]

CUTIS GYRATA OF UNUSUAL LOCATION. S. RUDBERG, Acta pædiat. **27**:67, 1939.

The term cutis gyrata refers to thickening, redundancy and plication of the skin in such a manner as to impart to the region affected an aspect suggestive of the appearance of the cerebral cortex; the anomaly bears a number of names. It was first described by Robert, in 1848. Subsequent publications have brought the number of reported cases to about 250. Middle-aged men appear to be most commonly affected. Since the commonest location of the lesion is the scalp, where long hair is apt to conceal it, it is probable that the frequency of its occurrence in women has been somewhat underestimated. It is said to be rare in children. The histologic features are sometimes those of inflammation, sometimes those of a nevus and sometimes merely thickening of the subepidermal connective tissue. Etiology and pathogenesis are obscure. It has been thought to bear some relation

to endocrine disorder, particularly to acrodynia. Some authors regard it as a manifestation of diverse causes and others as a degenerative consequence of advancing age. The analogy between cutis gyrata in man and the redundancy of the skin of the skull which characterizes certain canine species has led some writers to talk of atavism. In favor of its developmental origin is the fact that associated somatic anomalies are not infrequently present. Truffi described three varieties: (1) a congenital nevus, (2) an inflammatory lesion and (3) a congenital defect of development involving a disproportion between the skull and its integument, often associated with other anomalies. Fischer's classification contains the same elements.

The author reports the case of a newly born infant with cutis gyrata; the lesion involved the skin of the abdomen. A cutaneous scar suggestive of adhesion to the amnion was present on the right lower extremity and the ears were deformed. Autopsy revealed anomalies of the urinary tract and defects of the abdominal musculature. Microscopically, the gyrate epidermis was somewhat acellular and showed a deficiency of elastic fibers. In this case the lesion is interpreted as an anomaly of development. The bibliography is elaborate.

McCune, New York.

Surgery and Orthopedics

Cysts, Sinuses and Fistulae of the Thyroglossal Duct: Results in Two Hundred and Ninety-Three Surgical Cases. J. deJ. Pemberton and L. K. Stalker, Ann. Surg. **111**:950 (June) 1940.

Cysts of the thyroglossal duct may arise anywhere in the midline along the vestigial thyroglossal tract in its pathway from the base of the tongue to the region between the hyoid bone and the thyroid gland. Clinically the cyst occurs far more commonly below the level of the hyoid bone than above it. A series of 293 cases was reviewed, and 261 of the patients were satisfactorily traced as to the possibility of recurrence. Only 4 recurrences were noted. This result was in contrast to the 166 recurrences which were listed among the 261 patients before the last operation. The method employed is the modified Sistrunk operation. When a sinus is present, it is injected with methylene blue, and an elliptic transverse incision is made to include the sinus. The cyst is dissected free, the central portion of the hyoid bone is resected and the tissue up to the foramen caecum is cored out. The sex ratio in the cases reviewed was 2 males to 1 female. Operation was performed on only 32 patients who were less than 10 years of age. One hundred and forty-four patients were between the ages of 10 and 40; 90 were between 30 and 50 years and 27 beyond the age of 60 when the Sistrunk operation was performed.

H. M. Miller, Philadelphia. [Arch. Otolaryng.]

Dislocation of the First Cervical Vertebra. DeForest P. Willard and Jesse Thompson Nicholson, Ann. Surg. **113**:464 (March) 1941.

The dislocation may result from trauma, infection, paralysis or congenital defect. Traumatic dislocations are frequently associated with a fractured odontoid process.

The diagnosis is indicated by a few constant symptoms and signs and is verified by the roentgenogram. The head is held in torticollis position. The chin is frequently held tightly against the larynx. It is often difficult to open the mouth. Dysphagia and change in the voice may be observed. When rising the subject supports his chin in his hands. On attempted cervical motion, grating of the neck is experienced.

The authors report 6 cases and come to the conclusion that dislocation of the first cervical vertebra, except posterior dislocations or those occurring in the presence of neurologic complications, can be safely and easily reduced spontaneously with the head hanging dependent. This treatment is given in detail.

Bantin, Omaha.

THE ROLE OF MASSAGE AND PHYSICAL METHODS IN THE TREATMENT OF FRACTURES. CHARLES E. KINDERSLEY and JOHN BASTOW, Brit. J. Phys. Med. **3**:142 (Aug.) 1940.

Massage and physical methods in the treatment of fractures should teach the patient to help himself rather than allow him to remain a passive object.

HARTMAN, Cleveland.

Miscellaneous

MEDICAL APPLICATION OF ULTRAVIOLET RADIANT ENERGY. FRANK H. KRUSEN, Ann. Int. Med. **14**:641 (Oct.) 1940.

The author has made a careful analysis of the most important literature in this field. Among the many conditions in which ultraviolet radiant energy may be of value are: tuberculous peritonitis and enteritis, diseases due to calcium deficiency, secondary anemia and rickets.

GARD, Galveston, Texas.

INGESTION OF LARGE DOSES OF DILANTIN SODIUM. CHARLES D. ARING and MILTON ROSENBAUM, Arch. Neurol. & Psychiat. **45**:265 (Feb.) 1941.

The authors report the case of a 19 year old boy in whom acute intoxication not unlike that produced by alcohol developed after the ingestion of large doses of dilantin sodium—60 grains (3.88 Gm.) at one dose, 90 grains (5.82 Gm.) over a period of six hours and 105 grains (6.72 Gm.) over another period of ten hours. The same condition appeared another time, when he took 57 grains (3.69 Gm.) of the drug within a space of three hours.

BEVERLY, Chicago.

A MODERN NURSERY. ALFRED S. TRAISMAN and LOUIS J. HALPERN, Arch. Pediat. **57**:666 (Oct.) 1940.

A modern type of nursery for infants is described. Methods of minimizing cutaneous and cross infections are described. This result has been accomplished by strict isolation of infants and purification of the air through air conditioning, filtration and sterilization with ultraviolet rays.

ORR, Buffalo.

A QUANTITATIVE COMPARISON OF DIFFERENT ANALEPTICS. M. CHAKRAVART, J. Pharmacol. & Exper. Therap. **67**:153 (Dec.) 1939.

In practice the term is applied in the first place to stimulants of the medulla which act on the respiratory and vasomotor centers and in the second place to substances having an epinephrine-like effect, causing increased force of heart beat and arterial constriction. This work was done on mice, cats and pigeons, especially on mice. While mice probably react less like man than do dogs, the large number of mice that can be used excludes individual variations in reaction such as occur in dogs. Perhaps the most interesting features of the work are the author's observations on the distinction between a drug's ability to arouse mice from barbiturate narcosis and its action in lethal doses; as an example, benzedrine is the most important substance for arousing narcotized mice, but it is quite useless as an antidote for lethal doses of the same. Cardiazol and picrotoxin are not superior to strychnine in arousing narcotized mice, but they stand alone as antidotes in lethal effects. None of the drugs had any demonstrable effect on the vasomotor center. (While some of the drugs are powerful respiratory stimulants, especially ephedrine, benzedrine and lobeline, it is well to bear in mind that the respiratory center at different stages of depression acts in a variable manner to stimulation and the stage of depression is difficult to recognize, as was pointed out by Schmidt some years ago.)

PILCHER, Cleveland.

"A Cautious Experiment": The History of the New York Infirmary for Women and Children and the Women's Medical College of the New York Infirmary; Also Its Pioneer Founders (1853-1899). Annie Sturges Daniel, M. Woman's J. **46**:295 (Oct.); 335 (Nov.); 357 (Dec.) 1939; **47**:10 (Jan.); 40 and 62 (Feb.) 1940.

This "first medical charity established by physicians" was founded in 1857. One of the outstanding workers during the hard first two years was Dr. Marie E. Zakrzewska, who later (1862) founded the New England Hospital for Women and Children. The long article contains much on the history of the early administration of the hospital, biographies of the members of the first consulting staff and some material about the pioneers—Drs. Elizabeth and Emily Blackwell and Dr. Zakrzewska—and their unselfish devotion to their work. The reader learns of the problems of medical education, of nursing, and of the Civil War, but nothing of pediatric interest.

Rosenthal, St. Paul.

Water-Soluble Antihemorrhagic Compounds. S. Ansbacher, E. Fernholz and M. A. Dolliver, Proc. Soc. Exper. Biol. & Med. **43**:652 (April) 1940.

Methylnapthoquinone, or methylnaphthohydroquinone, is the most active vitamin K compound known. When administered intravenously in aqueous solution, it is as effective as when given by mouth in oily solutions. When it is given by mouth its potency is greater in water than in oil.

Hansen, Minneapolis.

Bromide Rash in a Nursling. A. Bernier, Union méd. du Canada **69**:20 (Jan.) 1940.

A 6 month old infant was admitted to l'Hôpital Notre-Dame because of a rash which had appeared two months previously. The lesions were typical of bromoderma. The mother had been taking "bromo-seltzer" daily for several years. As the baby had been weaned, no breast milk was available for analysis. Two siblings had been affected by a similar rash during the nursing period. The mother had noticed that during the third month of each of the three pregnancies a rash appeared on the inner aspect of her left leg. This rash disappeared some time after the termination of each pregnancy.

Daffinee, Boston.

The Mode of Action of Sulfanilamide. H. N. Green, Brit. J. Exper. Path. **21**:38, 1940.

Green has studied the mode of action of sulfanilamide and has come to the conclusion that its antibacterial effect is due to the inhibition of some enzyme reaction which is fundamental to bacterial reproduction. This enzyme reaction is normally catalyzed by a substance (P factor) which is extracted from bacteria. This factor in vitro can be shown to have a specific antagonistic action to sulfanilamide. The antibacterial action of sulfanilamide is evident when the depressing action of this drug is greater than the stimulating action of the P factor.

[Arch. Path.]

Defence Regulation Affecting Types of Electro-Medical Apparatus. Brit. J. Phys. Med. **3**:175 (Sept.) 1940.

Certain defence regulations have been adopted in the United Kingdom which forbid any person to use or possess high-frequency apparatus having an output of over 10 watts, except under permit of the Postmaster General. It has been proved that such apparatus causes interference with radio sets on the ground at distances exceeding 10 miles (16 kilometers) and with radio sets in aircraft flying at 10,000 feet (15.2 kilometers) at distances exceeding 50 miles (80 kilometers). This ruling applies both to short and to long wave diathermy apparatus but not to normal types of ultraviolet ray or x-ray apparatus.

Hartman, Cleveland.

REMOVAL OF A TERATOMATOUS "TWIN." VERNON PENNELL and L. C. MARTIN, Brit. M. J. **2**:414 (Sept. 28) 1940.

The child's teratomatous tumor on dissection showed evidences of being a second child. In other words, a "twin" was present in the teratoma.

ROYSTER, University, Va.

SULFANILAMIDE. ARTURIO SCROGGIE, Arch. d. Hosp. niños Roberto del Rio **9**:156 (Oct.) 1940.

The author completes his review on the various conditions in which sulfanilamide has been used.

SANFORD, Chicago.

CONTINUOUS INTRAVENOUS DROP INFUSION OF DEXTROSE SOLUTION. BERTHOLD EPSTEIN and OTTO SAXL, Jahrb. f. Kinderh. **149**:319 (Aug.) 1937.

The advantages of the continuous intravenous method of fluid administration are discussed with special reference to its use in cases of alimentary intoxication. Examples are given wherein the patients had severe reactions shortly following the institution of dextrose therapy. Somnolence, diminished heart tones and even convulsions are symptoms attributed to hypochloremia. This idea is substantiated by the experimental work to which the authors allude.

LANDAU, Hannibal, Mo.

Obituaries

SIR GEORGE FREDERIC STILL

1868—1941

Sir George Frederic Still, a pioneer in pediatrics in England, played a part in the development of medicine in his country comparable to that of Jacobi, Holt, Rotch and others in this country, which resulted in making the practice of the diseases of children a highly respected and important specialty. He entered practice at a time when the clinical acumen and experience of the physician was the only knowledge on which to base treatment. He lived to see scientific medicine develop and went through the transition from a time when the blood count was a highly scientific procedure to the present, when specialized knowledge is obtained from delicate laboratory procedures. He could walk through the wards and estimate the clinical status of sick children by merely looking at them and feeling their pulses with his delicately sensitive fingers. Many years of service and teaching in the Hospital for Sick Children, Great Ormand Street, W. C.; King's College Hospital; Infants' Hospital, Vincent Square, and Dr. Barnardo's Homes and Society for Waifs and Strays made his influence very widely felt.

He was a graduate of the University of Cambridge and the Murchison School of the Royal College of Physicians. He also delivered the Goulstonian Lecture in 1902, the Lumleian Lecture in 1918 and the Fitzpatrick Lecture in 1928. Among other honors it may be noted that he was the first president of the British Pediatric Association and president of the International Pediatric Congress in 1933. His interest in the prevention of infant mortality was expressed over a period of twenty years, terminating in 1937, during which time he was chairman of the National Association for Prevention of Infant Mortality. He received many honors both in England and in other countries, being made an honorary fellow of the Royal Society of Medicine in 1936, an honorary member of the American Pediatric Society in 1903 and of the Canadian Society for the Study of Diseases of Children in 1923, an honorary fellow of the Societa Medica Chirurgica of Bologna in 1934 and a corresponding member of the Société de Pédiatrie, Paris, in 1935.

His books have been widely read, the best known of them being "Common Disorders and Diseases of Childhood."

He was a delightful host, and it was always a privilege to be included as a guest in his household. He will be known in history as one of those pioneers who almost alone played an outstanding part in developing the science of pediatrics in England.

He was born in 1868 and died in 1941, at the age of 73 years.

Society Transactions

AMERICAN PEDIATRIC SOCIETY

THOMAS B. COOLEY, M.D., *President*

HUGH MCCULLOCH, M.D., *Secretary*

Annual Meeting, Hot Springs, Va., May 22-24, 1941

First Session

Thursday Afternoon, May 22

President's Address: Hereditary Factors in the Blood Dyscrasias. THOMAS B. COOLEY, M.D., DETROIT.

This article was published in full, with discussion, in the July 1941 issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN, page 1.

Cocarboxylase Content of Blood of Infants and of Children. DR. FREDERIC W. SCHLUTZ and ELIZABETH M. KNOTT, PH.D. (by invitation), Chicago.

This article was published in full in the February 1941 issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN, page 231.

DISCUSSION

DR. L. EMMETT HOLT JR., Baltimore: I should like to ask whether the authors made any measurements of the cocarboxylase content of the white cells. I understand that some observers have reported that most of the blood cocarboxylase is in the white cells.

I should also like to know whether they made any correlations between the thiamine content and the cocarboxylase content of the blood.

DR. FREDERIC W. SCHLUTZ, Chicago: We have not made any cellular studies. It is known that thiamine pyrophosphate is the type of thiamine which is contained in the cell which makes up a proportion of the cocarboxylase content of the blood. The ratio of this phosphorylated thiamine to free thiamine in the plasma is approximately 1:10. We have not checked these studies but I believe that Goodhart and others have obtained similar results.

As for the other question, I don't recall that such correlations have been determined.

DR. LEWIS WEBB HILL, Boston: One hears a good deal about vitamin B_1 deficiency in young babies. I, for one, haven't the slightest idea whether such a thing exists in America or, if it does, what the symptoms are. I should like to ask whether any one can describe the symptoms of vitamin B_1 deficiency (excluding frank beriberi, of course) in a young baby.

DR. FREDERIC W. SCHLUTZ, Chicago: Dr. Hill, I think that is difficult to do. Such symptoms are well recognized in the adult, and I think Dr. Knott's statements are quite dependable—she is a senior medical student now in addition to having received training as a chemist.

I believe that Dr. Russell Wilder, of the Mayo Clinic, has provided some good information on that subject. There is also some fairly definite evidence that in the older child the symptoms take the form of unusual fatigue, muscular weakness

and some hyperesthesia. The young infant who has less than 0.1 mg. of cocarboxylase per hundred cubic centimeters of blood is irritable. Of course, many infants who are malnourished are irritable, and it is difficult to say whether such irritability reflects vitamin B_1 deficiency. But I do think that cocarboxylase studies such as those reported here are informative and may possibly be as helpful as any other procedure in giving clues to the existence of depletion stages, or near deficiency stages. I don't think that any one has yet provided a clearcut definition of the clinical manifestations of vitamin B_1 deficiency. At least, I have not felt able to recognize them. But I think that if the diet is plainly deficient in vitamin B_1 and the level of blood cocarboxylase is low one has some information which is really worth while for making a diagnosis.

DR. FREDERICK TISDALL, Toronto, Canada: Am I right in assuming that Dr. Schlutz stated that the adolescent might need up to 5 mg. of thiamine per day? I ask that question because 5 mg. of thiamine is about 1,600 international units, and any one who has had experience in trying to construct a diet containing that amount knows that one must use a very special diet; it is extremely difficult, to get in over 600 or 700 international units in a daily diet.

DR. FREDERIC W. SCHLUTZ, Chicago: That figure of 5 mg. may be high. I don't know. It was computed proportionately from what we found the infant seems to require. It is possible that the older child can get along with less. We are putting this figure forward tentatively and not with any dogmatic assurance because we need more experimental work to support it. We are quite certain that we have correctly stated the minimum which the infant should have, either in his diet or in the form of a supplement, because of the rapidity with which his cocarboxylase level may decline.

DR. FREDERICK TISDALL, Toronto, Canada: May I ask again what requirements you determined for normal infants?

DR. FREDERIC W. SCHLUTZ, Chicago: Two tenths of a milligram in the food consumed daily is the requirement.

Is the Administration of Vitamin K to Newborn Infants of Clinical Value? DR. HEYWORTH N. SANFORD, DR. IRENE SHMIGELSKY (by invitation) and DR. JOSEPHINE M. CHAPIN (by invitation), Chicago.

Over a period of two years 1,693 newborn infants were observed during the first ten days of life. Vitamin K was administered to 711 of these infants. In 606 determinations of plasma prothrombin it was found that the prothrombin content of the plasma of the cord blood of the normal infant was similar to that of its mother's plasma. During the neonatal period the plasma prothrombin diminished during the first, second and third days of life, in descending proportions. It increased during the fourth, fifth and sixth days of life, and almost had the value for the cord blood plasma from the seventh day throughout the rest of the neonatal period. We did not find that the values for plasma prothrombin of the normal newborn infant were influenced by the parity of the mother, the season of birth, the type of delivery (including the induction or lack of induction of anesthesia in the mother), the weight of the baby or the type of feeding during the neonatal period.

The value for the plasma prothrombin of the normal newborn infant could be increased above that for the cord plasma by the administration of vitamin K to the infant. The plasma prothrombin of the mother and the cord plasma prothrombin of the infant were both increased above normal values by the administration of vitamin K to the mother before the birth of the child. The values for plasma prothrombin of infants who were given vitamin K or whose mothers were given vitamin K before delivery were well above those of normal infants throughout the neonatal period.

However, the administration of vitamin K did not affect the frequency of hemorrhagic manifestations. There were just as many instances of melena and of conjunctival, vaginal, petechial, cerebral and umbilical hemorrhages and cephalhematoma in the one group as in the other. The percentage mortality for the two groups was the same.

During this same two year period 93 premature infants were observed. Of these, 48 were given vitamin K at birth. We did not observe any more hemorrhagic disturbances in the one group than in the other. The mortality for the two groups was essentially the same, and the only cerebral hemorrhage which occurred in either group was in an infant given vitamin K.

There were no hemorrhagic manifestations in any of the infants in either of the groups of full term or premature infants in which the coagulation time of the whole blood was increased over normal (five minutes). As judged by this standard, the rate of occurrence of hemorrhagic disease of the newborn among our patients for the last ten years has been 1 in 2,500.

DISCUSSION

DR. T. J. HUMPHRIES, University, Va.: I wish merely to present some clinical data obtained by Dr. W. W. Waddell Jr. at the University of Virginia Hospital. The slide is more or less self explanatory. (Slide.) On the left are data on the untreated patients and the types of bleeding which occurred, such as bleeding from the cord alone and bleeding from circumcision alone. The incidence of bleeding in this group was 10.4 per cent. The mortality from intracranial hemorrhage was 1.3 per cent in 219 cases.

On the right are data for the treated patients. Treatment was given to the mother, to the baby or to both. There were 12 instances of bleeding, of which 6 were cephalohematoma and 6 of intracranial hemorrhage. Only 1 of the 12 affected infants showed any prothrombin deficiency. In 4 cases of this group autopsy showed intracranial hemorrhage. The incidence of bleeding in this group was 1.07 per cent, and the mortality from intracranial hemorrhage was 0.35 per cent.

DR. GEORGE M. GUEST, Cincinnati: I should like to ask for further details concerning the effects of diet during the neonatal period on the changes in levels of prothrombin in the blood which are found during this period.

At the recent meeting of the Society for Pediatric Research in Atlantic City, Dr. Gellis and Dr. Lyon, of Cincinnati, reported on studies of prothrombin levels in the blood of breast-fed and artificially fed infants during the neonatal period. The infants who were given only breast milk during the first few days showed changes in prothrombin levels approximately the same as those demonstrated by Dr. Sanford in the chart representing untreated patients. However, the infants who were given supplementary feedings of evaporated milk early showed a rapid rise in the prothrombin level. While this phenomenon is unexplained, it seems important to evaluate carefully the possible influence of diet in all investigations of this sort.

DR. STEWART H. CLIFFORD, Boston: I have a few figures from the Boston Lying-in Hospital which may be of interest in conjunction with the results that Dr. Sanford has reported. My associates and I have a control series of 1,603 babies who did not receive vitamin K at birth and a series of 629 newborn infants who were given synthetic vitamin K as soon after delivery as possible.

I shall not take time to detail our observations, because they are practically identical with those just reported by Dr. Sanford, with the exception that we did not encounter any hemorrhagic disease among the 629 infants in the group given vitamin K. Our definition of hemorrhagic disease is the same as that Dr. Sanford gave. However, I must point out that our experience would lead us to expect only 2 cases of hemorrhagic disease, as we define it, in this group of 629 patients. Therefore the series is much too small to be of any statistical significance.

In our control group of 1,603 babies we did encounter 5 instances of hemorrhagic disease, which agrees with our expected incidence of 1 in 300. It is of interest that this is the incidence Dr. Sanford found for his series when he used our definition of hemorrhagic disease.

I have one other point. The apparent discrepancy between the incidence of hemorrhagic disease reported in the University of Virginia group on the one hand and in the Boston and Chicago groups on the other may be due to the different types of patients encountered. The former group is composed to a large extent of infants delivered at home; I suspect that there was a high incidence of Negro patients of a relatively low economic level and that the mothers may not have appeared early enough in pregnancy to receive adequate antepartum care. In the Boston group the situation was quite different: All of the patients were delivered in a hospital, all of the mothers had adequate antepartum care and none were charity patients.

At the moment, one of the pediatricians from Virginia who helped compile the statistics giving the incidence of bleeding in the Virginia group as 10.4 per cent is working in the pediatric service of the Boston Lying-in Hospital. He has informed me that from his observations in the two places he has concluded that there is strikingly less hemorrhagic disease of the newborn in Boston than in the South. My point is that all of the groups have reported statistics which are accurate for the conditions in their own geographic locations and that the differences encountered may be due to differences in environmental, social and medical factors in the various places.

I should like to ask Dr. Sanford whether he has any idea why long before the discovery of vitamin K hemorrhagic disease had begun to disappear.

DR. A. ASHLEY WEECH, New York: The message from Dr. Sanford is both instructive and disturbing. The disturbing element comes from results which on first thought do not seem to agree with observations at the Babies Hospital but which on second thought bring the realization that diverse results may be an expression either of differences in the infant populations studied or of differences in the technics employed.

The work to which I should like to refer is that which Dr. Pray, Dr. McKeown and Dr. Pollard have been conducting in the maternity wards of the Sloane Hospital. Dr. Pray and his associates have recorded the incidence of retinal hemorrhages in newly born infants who received no vitamin K, in infants whose mothers received vitamin K during labor and in infants whose mothers received vitamin K before the onset of labor. In the control group, whose mothers received no vitamin K, there were retinal hemorrhages in 45 per cent of the infants. In the group whose mothers received vitamin K during labor, the incidence of retinal hemorrhages was 20 per cent. And in the group whose mothers received vitamin K before the onset of labor, the incidence of retinal hemorrhages was 13 per cent. I have examined these figures from the statistical standpoint. The difference between 20 per cent and 13 per cent cannot be accepted as significant, but between the two groups of infants, those who did not receive vitamin K and those to whom vitamin K was administered by treatment of the mother, the difference was highly significant. There can be no doubt, then, that in New York, at least, the administration of vitamin K does lower the incidence of retinal hemorrhages.

DR. L. EMMETT HOLT JR., Baltimore: May I add a word as to Dr. Hellman's experience in Baltimore? The experience has been that vitamin K given to the mother before labor greatly decreases the incidence of retinal hemorrhages. This discrepancy does not in any way detract from Dr. Sanford's results. It seems likely that differences in the time and in the technic of the administration of vitamin K may have been responsible for the differences in the clinical results.

DR. RANDOLPH K. BYERS, Boston: I wonder if there isn't a point of confusion here. There must be some differences in the way the babies are handled in the different places. There is the factor of trauma, and there is the factor of

the blood. I do not have enough experience to separate the two factors, but it seems to me that both must have played some part in these series of cases of hemorrhagic disease and must be taken into account.

DR. HEYWORTH N. SANFORD, Chicago: Dr. Humphries has given you another side of this problem, which I believe Dr. Clifford has commented on better than I could. In answer to Dr. Guest's question of the difference between the prothrombin values for artificially fed and breast-fed infants, of the babies in our normal control group 627, or 64 per cent, were entirely breast fed. To these infants nothing was given except water in addition to what milk could be obtained from the mother's breast during the first seven days of life. The feedings given the 355 infants (36 per cent) of the normal control group who were artificially fed from birth consisted in the majority of instances of evaporated milk, water and carbohydrate. We found no difference between the prothrombin values for the two groups. I might state that this problem was studied rather carefully, because Salmonsen has reported that he did not observe any hemorrhagic disease among more than 1,000 infants who were given cow's milk formulas during the first two days of life.

While I have no doubt that different factors operating in various localities make for a discrepancy in the reported incidences of hemorrhagic disease, I believe that the greatest problem is in deciding just what is hemorrhagic disease. You will observe that while Dr. Clifford and I do not quite agree on the definition of hemorrhagic disease, when we both used the same classification we had exactly the same number of instances. I absolutely agree with Dr. Clifford that 1,600 newborn infants are too few to allow one to draw any definite conclusions about hemorrhagic disease of the newborn. I rather apologize for reporting on such a small number, but I have been greatly disturbed by recent articles in the literature in which 30 or 40 cases have been reported and conclusions have been drawn on hemorrhagic disease of the newborn. I thought it might be well to give the results of at least one series of studies in which over 1,500 newborn infants were observed.

In answer to Dr. Clifford's question as to the decrease in hemorrhagic disease over the last two decades, I believe that this is due to two factors. The first is better antepartum care and better care of the newborn infant. The second is that most physicians now realize that hemorrhagic disease of the newborn is really a syndrome and not a disease and that it has many etiologic factors. Such conditions as sepsis, congenital syphilis and erythroblastosis, which twenty-five years ago were all called hemorrhagic disease, are now recognized as separate entities.

As for retinal hemorrhages, I have been observing them in newborn infants for the last fifteen years, and it seems to me that one can find them in almost all newborn infants if one looks long enough. I have been criticized so much for observing them when no one else could that I have included in this series only instances of conjunctival hemorrhages, which every one can see.

The Influence of the Antepartum Diet on the Infant. DR. J. HARRY EBBS, Toronto, Canada (by invitation).

Studies have been made on the influence of good and poor antepartum diets on the health and the obstetric course of 400 women and their offspring. Ninety women found to have poor diets and low incomes were supplied with certain essential foods daily throughout the latter half of pregnancy. Each diet record was analyzed in order to determine as closely as possible the amount of the individual food components received by the mothers. Studies of the blood phosphatase, vitamin C level and hemoglobin content were made at intervals on both the mother and the child. Clinical observations and the laboratory investigations indicated that the antepartum diet had a striking influence on the health

of the mother during pregnancy, labor and convalescence. The diet during pregnancy also markedly affected the health of the child during the first few months of life.

The incidence of miscarriage, prematurity and stillbirths was much less among the mothers supplied with a supplemented antepartum diet. The number of mothers who were able to nurse their infants successfully was higher in the group given a good diet. The condition and the progress of the baby in the hospital was better when the mother had received a good antepartum diet. The average birth weight of the babies whose mothers received a poor diet was slightly higher than the average for the infants whose mothers received extra food. When examined at 6 months of age, the babies born of mothers given a good or supplemented diet were found to weigh more, to be in better general health and to have suffered fewer illnesses than the other group of infants. There were more deaths from infections in the group whose mothers received a poor diet.

Studies of phosphatase in the mother's blood have indicated the value of administering vitamin D in pregnancy.

DISCUSSION

DR. WILLIAM W. SWANSON, Chicago: I am much interested in this paper, because during the last ten years I have made a similar study, using an entirely different approach.

In 1930, while working at the Harriet Lane Home, I found on analysis that the offspring of rats given supplements of vitamin D had considerably more calcium and phosphorus than the offspring of rats which consumed lesser amounts of vitamin D.

A few years after I published my observations, Sontag and co-workers showed by analysis that the offspring of rats which were on a diet deficient in calcium and phosphorus but had an increased consumption of vitamin D had a calcium and phosphorus content nearly equal to that of the offspring of rats on an adequate diet. Similar studies have been carried out on cattle and on pigs. Apparently, then, from animal experimentation, there is available considerable information as to the influence of the maternal diet on the offspring.

One other interesting observation from the study on the offspring of rats is that rats given extra vitamin D during pregnancy were no larger, in fact, were on the average a little smaller, than those of rats not given vitamin D.

Recently, Dr. Dieckmann and I had the opportunity to analyze the body of a prematurely born infant who died soon after birth. This infant's mother had been on a controlled diet. The analyses showed a calcium and phosphorus content from 15 to 20 per cent greater than the content of the fetuses of the same age that were used as controls.

It appears from a study of animal experiments and the little support given by analyses of fetuses that vitamin D and an adequate mineral diet play a considerable part in the betterment of the offspring. I think Toverud was right when she said it is not only necessary to take care of the infant's nutrition from birth but is very important to consider the nutrition of the mother during pregnancy.

DR. C. ANDERSON ALDRICH, Winnetka, Ill.: I think Dr. Ebbs has brought up a very important subject. My interest in it was first aroused about fifteen years ago, when I was given my first service at the cribside pavilion in Children's Memorial Hospital and saw many little babies. I tackled the job with a lot of enthusiasm and found that I wasn't getting anything like the results with those babies that I got in private practice. I examined the diets of the mothers and I don't think that any pediatrician would have considered them adequate. The supply of vitamins A, C or D is not the whole question; it seems to me that one must be concerned with the adequacy of the whole diet that the mother gets—good babies simply aren't made out of poppyseed rolls and coffee.

DR. ARTHUR F. ABT, Chicago: If I understood the slide correctly, Dr. Ebbs gave about 4½ ounces (133 cc.) of tomato juice a day. I was interested in Dr. Swanson's discussion of vitamin D in the diet, and I desire to discuss vitamin C. Four and a half ounces of tomato juice isn't very much. If one is liberal, one will say that there is 3 mg. of vitamin C in 1 ounce (30 cc.) of canned tomato juice, and that, as I figure it, is only about 12 or 15 mg. of vitamin C a day.

Some investigators in Boston have stated that the fetus is a parasite so far as vitamin C goes. All that means to me is that if the mother doesn't get enough ascorbic acid, the fetus doesn't get enough; and I think that this small supplement of tomato juice was not very generous.

DR. FREDERICK F. TISDALL, Toronto, Canada: I have had the opportunity of watching this work of Dr. Ebbs during the past three years, and it really is a fascinating study. My associates and I in Toronto have been accused of trying to build up a case for the pediatricians. Times were bad with us. We extended the age limit for our patients one way to about 18 years, and we are now being accused of extending it the other way about five months, but really the pediatrician must start in to look after his baby before it is born or else educate the obstetrician to do so. The difference in the babies of Dr. Ebbs's study was so striking that if one lined up a dozen of them between 6 and 8 months of age and asked a nurse from the clinic to pick out the 6 best ones she would be 75 per cent correct in selecting babies who were born of mothers who had been well fed.

There is another point which is of considerable interest from a governmental standpoint. Dr. Ebbs didn't mention the cost of this diet, but the cost of giving these mothers additional food was about $25 for the period of observation. There were 120 mothers in the poor diet group; if they had been well fed it would have cost a total of $3,000. There were 14 infant deaths in that group and no deaths in the other group; so that puts a value on a baby's life of $215. Apparently, for $215 one can save a baby's life.

As a taxpayer at home I object very much to feeding a man so well on relief that he won't work, but there is no argument about whether the state should take the responsibility of seeing that pregnant women are well fed. I think from a governmental standpoint that it is very important.

I have some figures here pertinent to Dr. Abt's question, if Dr. Ebbs will allow me to mention them. Dr. Abt asked about the tomato juice. The vitamin C content of 4½ ounces of tomato juice would run a little over 20 mg., between 20 and 25 mg. One orange in addition gave about 40 mg., or a total of 60 mg. a day, which in addition to what the mother was already getting made a fairly good daily intake of the vitamin.

DR. GEORGE M. GUEST, Cincinnati: It seems appropriate to recall here the important work of Strauss and Castle, reported in 1933, on anemia in infancy due to maternal iron deficiency during pregnancy. They demonstrated a high incidence of nutritional anemia at the age of 1 year among infants born of anemic mothers, as compared with the incidence observed among infants born of nonanemic mothers, although there was no significant difference between the two groups of infants at birth. Since then many other investigators have reported similar experiences and have pointed out the need for supplementing the mother's diet with iron when she is anemic. Using criteria for definite anemia, however, the "borderline" case may be neglected. Perhaps it should be emphasized that there is much variability displayed in the tendency for anemia to develop during pregnancy even when the diets appear to contain adequate amounts of iron.

DR. J. HARRY EBBS, Toronto, Canada: If I may answer Dr. Guest's question first, every woman found to have a hemoglobin content below 70 per cent was given iron by the obstetrician automatically, and the wheat germ which we supplied to the group given supplements contained an additional amount of iron.

Dr. Swanson's remarks on the studies on calcium and phosphorus in rats and the administration of vitamin D are very interesting. My associates and I have been asked many questions about the administration of vitamin D in pregnancy. One of the most interesting things we discovered was that by giving capsules of viosterol in oil to one group we were automatically giving them a little bit of psychologic lift; so we had similar-appearing capsules containing plain corn oil given to the control group. The psychologic effect was shown by the fact that when the interns, who had helped themselves to the capsules, left the service, they informed us that they had felt much better while taking them. They had been taking plain corn oil for weeks!

We carried out a considerable amount of laboratory investigation and found that the vitamin C level was raised in the mother's blood and in the cord blood as a result of giving supplements of orange juice and tomato juice, in addition to what the mother could supply in her diet from her own income.

Studies on the Self Selection of Diets. Dr. Curt P. Richter, Baltimore (by invitation).

The following results were obtained from studies in which rats and human beings selected their own diets: 1. A close relation exists between appetite and dietary needs. 2. Rats make beneficiary dietary selections from purified substances, such as mineral solutions and the crystalline members of the vitamin B complex, and grow as well as, or even better than, when they are given a natural food diet. 3. In the self-selection technic there exists a new tool for the investigation of a variety of nutritional problems. (Up to the present the results have been largely confirmatory of biochemical studies. It is hoped that in the future this method may point the way to new biochemical relations.) 4. Human beings, especially patients with Addison's disease, may make similarly beneficial choices. 5. All of the dietary self-selection activities of rats or of human beings may be regarded as responses of the total organism by means of which a constant internal environment is maintained.

DISCUSSION

Dr. Frederic W. Schlutz, Chicago: All animals do not seem to make such biologic selection. At the moment I have a dog under my care which was passed on to me by the Wilson Laboratories. This dog underwent bilateral adrenalectomy and has been kept alive with proper treatment, such as the administration of salt solution and, occasionally, adrenal cortical extract.

This dog has been offered an opportunity to do the kind of thing Dr. Richter's rats did. His very life depends on the ingestion of salt solutions, especially solution of sodium chloride, but when such solutions were placed within his reach they were not taken voluntarily but generally had to be given by tube.

This was a consistent experience. He is a police breed, ordinarily regarded as very intelligent, and is smart and cooperative in many ways. He runs well on the treadmill and some interesting observations have been made on him, but this particular thing he will not do. All animals do not seem to select food on the basis of biologic needs.

Cerebral Anoxia of the Newborn. Wyman C. C. Cole, Detroit (by invitation).

"Birth injury" has long been recognized as a cause of neonatal death and of permanent injury to the nervous system. It has usually been thought of as hemorrhage or direct injury. Recent evidence indicates that many of such injuries are the result of anoxia.

Illustrative cases are presented which demonstrate the lesions produced by anoxia.

The causes of cerebral anoxia in the newborn are discussed and its relation to asphyxia emphasized. Particular reference is made to the effects of the analgesics and anesthetics given the mother.

DISCUSSION

DR. WARREN R. SISSON, Boston: I have been interested for some time in the general subject of anoxia. I want to call attention to the fact that although analgesics and anesthetics are important factors in the production of anoxia, in some cases the baby breathes well for a few seconds or a few minutes and then a severe form of asphyxia develops, even though the mother had received no anesthesia, except spinal anesthesia, and no drugs, such as pentobarbital sodium or barbiturates. The anoxia in such cases must be due to some metabolic factor which is probably associated with preeclamptic toxemia.

I have frequently observed such anoxia in the babies of diabetic mothers, and I should be much interested to know whether Dr. Cole has seen this type of anoxia.

DR. BRONSON CROTHERS, Boston: I think that this is a most important series of observations. My experience has been gathered in a community where analgesia is widely used, and my clinical impression is that there are fewer handicapped babies born now than before it was used. I feel perfectly clear on that point.

Whether Dr. Cole is willing to say that the prolonged apnea, or the prolonged inability to breathe, produces a reversible or an irreversible lesion seems to me the nub of the whole thing. Obviously, if he can measure the effect on the brain by the timing of the initiation of respiration he has a complete case. Otherwise, I should think the clinical experience might still be valid, and so far as I have observed in Boston, I feel that the use of analgesic drugs has led to a better group of babies.

DR. STEWART H. CLIFFORD, Boston: I should like to question whether Dr. Cole is quite right in referring to the various degrees of retardation in breathing after birth as stages of "asphyxia." Last year Dr. Clement Smith at a meeting of this society presented the results of a study on the effects of ether, among other drugs, on the responses of the infant at birth, and he demonstrated by studies on the blood that the baby was slow in responding not because he was suffering from lack of oxygen, or asphyxia, but because he was anesthetized. This difference in interpretation of this symptom at birth is the reason that in our results my associates and I have not been able to make out the same case against pentobarbital sodium, for instance, that Dr. Cole has. I wonder whether his "asphyxiated" infants do not include two groups, one the truly asphyxiated babies and the other the slowly responding, anesthetized babies. They are two entirely different groups. In the new series which Dr. Cole is studying, that factor undoubtedly will be controlled.

Furthermore, one suspects that in the cases in which six or seven doses of scopolamine hydrobromide was given, in those in which there was prolonged administration of ether and in those in which large doses of pentobarbital sodium were employed there must have been some obstetric factor which of itself might have influenced the babies and made them slow to respond. It seems likely that if the obstetric conditions had been entirely normal an average amount of medication would have been employed before the birth of the baby.

We feel, as Dr. Crothers has stated, that the proper use of analgesia has an important place in modern obstetrics. Prior to 1934 no analgesia was used at the Boston Lying-in Hospital. After 1934 it was used in practically every delivery. The stillbirth rates and the neonatal mortality rates in this hospital have both shown marked reductions since 1934. We shall be looking forward to Dr. Cole's new study, in which these various factors I have mentioned will undoubtedly be controlled.

DR. L. EMMETT HOLT JR., Baltimore: I noticed something rather curious in Dr. Cole's data which I should like to ask him about. As the dose of sedative increased, the incidence of spontaneous breathing decreased, which one might well expect, but the rate of stillbirths gradually dropped. That seems to me a rather surprising phenomenon, and I wonder if he has any explanation for it.

DR. WYMAN C. C. COLE, Detroit: As to Dr. Sisson's question about the other factors causing asphyxia, this presentation was only a minor part of the whole study. By far the most important single factor next to prematurity is the trauma of labor, which could have been shown if I had had more time; also, obstetric operations and dystocia of all forms have an important influence. Illness of the mother is a very important factor. Those cases in which such factors were present were segregated and studied separately.

Anoxia is a very complicated problem, and it is impossible to gather a group of cases in which only one factor is operative. One must always consider the combined effects of the trauma of labor, the health of the mother, the age of the mother, the duration of labor and the anesthetics and the sedatives used.

The effect of anoxia on the brain, which Dr. Crothers referred to, was what I really intended to talk about today, but Dr. Johnston, who invited me to speak at this meeting, requested that I present this particular aspect of the subject again. I think the effects of anoxia on the brain have been fairly well shown by a number of investigators, particularly Yant, Courville and Waters, of the University of Wisconsin, and Steiner. It has been fairly well shown that the maximum length of time which brain cells can exist without oxygen is about four minutes and that frequently irreversible changes occur in as short a time as one minute; in certain conditions, such as dehydration and hypoglycemia, as short a time as fifteen or twenty seconds may be sufficient to produce death of the brain cells. This has been thoroughly demonstrated, I think, both clinically and experimentally.

I am not very familiar with the type of spinal anesthesia used. The obstetricians decided about that, and I don't know what they use. Incidentally, they are not as keen about it as they were, because in about 1 of every 90 or 100 deliveries they have had a disastrous experience with spinal anesthesia. The trend is toward local anesthesia.

In regard to Dr. Holt's question, the incidence of stillbirths is probably of no significance except in a few groups. There were only 92 stillborn infants among 5,000 babies. At least half of those were due to some form of congenital malformation, so that as small a figure as that, even in a series of 5,000, is not statistically significant.

Dr. Clifford questioned my referring to the various stages of asphyxia. It is very difficult to determine when a baby is severely asphyxiated and when it is mildly asphyxiated. Such determinations were made on purely clinical grounds. A baby who had to have active resuscitation with administration of artificial respiration and oxygen, and who took several minutes to come around was classified as severely asphyxiated. If the same procedures were carried out but the baby responded more quickly, it was classified as mildly asphyxiated.

In the study now in progress a stopwatch is used to keep track of the time at which the baby takes its first gasp, when it first cries and when respiration is definitely established. I can say that in the normal baby respiration is definitely established within ten seconds after it is born. A delay of as long as thirty seconds is probably pathologic.

Postnatal Readjustments of the Red Blood Cells in Individual Infants. DR. ALFRED H. WASHBURN, Denver.

This paper will be published in full, with discussion, in a later issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN.

Congenital Tracheoesophageal Fistula. DR. F. P. GENGENBACH and DR. E. I. DOBOS, Denver (by invitation).

This interesting congenital anomaly is ordinarily associated with congenital atresia of the esophagus, but it may occasionally occur in infants who show little, if any, esophageal obstruction. There is little reference in the literature to the latter type.

The earliest publications describing such anomalies were those of Sir Morrill Mackenzie, in 1880 and 1884, but Mackenzie referred to a case reported by Durston in 1670.

Congenital atresia of the esophagus apparently may appear very early in embryonic life, as there are references to this condition in an embryo only 18 mm. long, in another 9 mm. long and in a third only 8 mm. long. Various theories of its embryonic formation are discussed.

Vogt has probably given the most practical classification of the various types of congenital atresia of the esophagus, both with and without associated tracheoesophageal fistula. By far the most frequent type (3b) is that in which the upper segment of the esophagus ends in a blind pouch and there is a fistula connecting the trachea and the upper portion of the lower segment of the esophagus. Seven of the 9 proved cases contained in this study were of type 3b, and in the other 2 cases there was a congenital tracheoesophageal fistula but little, if any, obstruction in the esophagus. Another patient suspected of having the latter type of the disorder, though it is not yet proved, and who is now under observation is also reported on.

Characteristic symptoms, which occur shortly after birth, are attacks of choking and coughing, appearance of frothy mucus in the mouth and nostrils and cyanosis. The infant is unable to nurse at the breast, and attempts at other methods of feeding cause an exacerbation of the foregoing symptoms. Passage of a very small, soft rubber catheter through the mouth or nose soon meets with an esophageal obstruction. Objections to the use of radio-opaque substances, such as barium and iodized oil, for roentgen diagnosis are discussed. Differential diagnostic signs and symptoms of the various types of the anomaly are given.

Treatment of acute symptoms is by aspiration and by the administration of oxygen and other respiratory and circulatory stimulants. Supportive measures to prolong the life of the infant include blood transfusions, phleboclysis, to combat dehydration, and feedings through a catheter in the stomach. In cases without esophageal atresia, treatment of acute symptoms is the same, but chemotherapy is also necessary to combat the recurring infections of the upper respiratory tract.

In the majority of the reported cases the patient died within the first week of life. Reference to patients who lived longer is made. Death is usually due to bronchopneumonia.

Very early surgical intervention apparently offers the only hope for ultimate survival in cases in which there is associated atresia of the esophagus. All reported methods of surgical procedure have so far been rather disappointing.

A detailed report of the small number of cases in this survey, which contains an unusually high percentage in which there was no esophageal atresia, is given. This survey differs from other reports in the great preponderance of patients of one sex.

Second Session

Thursday Evening, May 22

Adrenal Androgenic Tumor in a Female Infant. DR. FRANK C. NEFF, DR. GEORGE A. WALKER (by invitation), DR. GALEN TICE (by invitation) and DR. NELSE F. OCKERBLAD (by invitation), Kansas City, Mo.

A moving picture in color was exhibited, showing the physical characteristics of this infant girl, which developed in the period of 8 to 16 months of age. The laboratory and other diagnostic data are given, and the observations at operation and the postoperative course are discussed. The symptoms of hirsuties, paroxysmal

hypertension, acne and hypertrophy of the labia and the clitoris receded within a few weeks after removal of the tumor, as was shown by the later pictures. The child recovered.

The tumor, which weighed 96 Gm., was found to be a chromaffinoma of the medulla; it apparently had not invaded the cortex, though one cannot yet rule out the danger of later metastasis and malignancy. The observations are difficult to explain on the basis of a medullary tumor because they belong to the adrenal cortex syndrome. Mechanical effects or a perverted type of hormone may be the cause.

Girls with this syndrome, in particular, are likely to exhibit pseudosexual precocity rather than the type of precocity produced by ovarian growths.

DISCUSSION

DR. FRITZ B. TALBOT, Boston: Of course, the most important factor in dealing with cases like this is to decide beforehand whether the tumor that one is dealing with is benign or malignant. In this respect much information can be obtained by measuring the absolute amounts of the urinary androgens and estrogens. Apparently, there is a great difference between the amount of hormone secreted when the tumor is benign and the amount secreted when it is malignant. In the few cases of malignant tumor which have been studied, the amount of hormone secreted was 1,000 per cent greater than in the cases of benign tumor.

Muscular Dystrophy from the Nutritional Standpoint. DR. ANN MINOT (by invitation) and DR. KATHARINE DODD, Nashville, Tenn.

Five patients with typical pseudo hypertrophic progressive muscular dystrophy were treated over a period of several months with large amounts of vitamin E. Two showed unmistakable clinical impovement, while no effect was noted on the other 3. There are many points of similarity between progressive muscular dystrophy and the degenerative changes in muscles which occur in animals deprived of vitamin E. However, patients with muscular dystrophy exhibit no apparent dietary lack or inability to absorb vitamin E. If a deficiency exists it appears that it must be secondary to some unusual demand or to the presence of some factor antagonistic to the biologic action of alpha tocopherol. Shute has reported that the resistance of blood serum to tryptic digestion is increased in subjects with a dietary lack of vitamin E and in women with a deficiency in vitamin E secondary to the excretion of excessive amounts of estrogenic substances. Increased resistance to proteolysis was found in the serums of patients with muscular dystrophy, as compared with the serums of normal children. However, we failed, as others have, to show increased resistance in the serums of animals with simple vitamin E deficiency. On the basis of Shute's alternative suggestion we studied the output of estrogenic substances in the urine of 7 patients with muscular dystrophy. Extracts from 1 liter of urine from each of these patients injected into castrated mice always produced vaginal estrus in the majority of the test animals. Similar extracts from the urine of boys of similar age without muscular dystrophy failed to produce estrus in any test animal.

The increased output of estrogenic material was exhibited both by the untreated patients and by those receiving vitamin E therapy. While it is not yet possible to fit these various observations into any single working hypothesis, it appears likely that endocrine dysfunction is an important primary or secondary factor in muscular dystrophy. The occasional effectiveness of vitamin E therapy may well be due to an effect on the endocrine system. Possibly such medication is an uncertain and inefficient means of accomplishing what some day can be done more effectively with an appropriate hormonal agent.

DISCUSSION

DR. KATHARINE DODD, Nashville, Tenn.: When we first decided to present this paper we were apparently having success with the treatment of muscular dystrophy with vitamin E. It had seemed to me that little boys with the condition, who were

not sick at first but who, one knew, must become progressively crippled as time went on, were most pathetic patients. Although according to some textbooks children with muscular dystrophy sometimes show improvement, I had never until we started using vitamin E therapy seen any sign of improvement in any one who had the disease; there was always a steady progression of weakness and disability. The first patient we treated with large amounts of vitamin E undoubtedly improved during his first month of treatment. The father brought us the child's brother, who was just beginning to fall frequently and had become unable to rise from the ground. The younger child regained practically normal muscular strength under treatment.

At the time of our early therapeutic use of vitamin E the few reports of clinical trial of vitamin therapy in cases of muscular dystrophy were so encouraging as to be difficult to believe. It seemed that severely damaged muscles could not, with any form of therapy, start to function as nearly normally in so short a period. The majority of later reports have stressed the entirely negative results which have been obtained with vitamin E therapy.

As we treated more patients we also met some who failed to respond with improvement in muscle function. Dr. Minot, while trying to find an explanation for our apparent therapeutic successes, discovered that our boys with muscular dystrophy all had a substance in their urine which when extracted and injected into castrated mice produced estrus. We hope that we may have a lead as to a possible cause of muscular dystrophy in some kind of endocrine disturbance. Perhaps ultimately we may through following this lead be able to find a form of therapy more consistently beneficial than treatment with vitamin E.

Clinical and Anthropometric Observations on the Circus Midget. DONOVAN J. MCCUNE, KATHARINE K. MERRITT (by invitation) and JOSEPHINE H. KENYON (by invitation), New York.

It is difficult to prevail on the professional midget to submit to scientific inquiry. The reasons for this attitude appear to be a sort of paradoxic shyness combined with prudery and a protective stance toward the details of their physical structure, which they regard as a trade secret. Their hesitancy is abetted by their managers, who are reluctant to risk revelations which, although not without advertising value, might have the effect of parting the veil of exaggeration and mystery which is maintained between the performers and the lay spectators. It follows that the number of clinical observations on professional midgets is small. Dupertuis made anthropometric measurements of 85 members of the troupe which was exhibited at the Chicago world's fair in 1934. These unpublished data reveal that the mean height of the men was 124 cm. (50 inches) and of the women 119 cm. (48 inches), values which are about 25 per cent below the corresponding averages for American adults. Ecke (*Fortschr. a. d. Geb. d. Röntgenstrahlen* **60**:107 [Aug.] 1939) made similar measurements of 11 Lilliputians and in some instances supplemented the superficial observations with roentgen and restricted physical examinations. The results were highly instructive. Aside from Ecke's study, the medical literature contains only isolated descriptions of single midgets whom observers were fortunate enough to persuade to cooperate in supplying fragmentary information.

Our observations concern 7 persons. Of these, 6 earn their living by participating in exhibitions, and the seventh was a professional midget until a sudden access of growth resulted in the attainment of a stature that excluded him from this role.

Two of the subjects are brother and sister, of Italian parentage. When first studied the male member was 16 years of age and 108 cm. (43 inches) in height and weighed 20 Kg. (44 pounds). Skeletal maturity was equivalent to that of a 10 year old child, and dentition was somewhat retarded. At 25 years of age his height is 120 cm. (48 inches) and his weight 38 Kg. (84 pounds). The skeleton is of adult attainment, and 28 teeth are present. Although his genital organs are

those of an adult and sexual appetite is alleged to be present, potency has apparently failed to develop. The sister has been kept under close observation from the time she was 3 years old, when she was 53 cm. (21 inches) tall and weighed 6 Kg. (13 pounds), until her present age of 13½ years; her height has increased to 75 cm. (30 inches) and her weight to 11 Kg. (24 pounds). Although her physical dimensions have remained those of a 1 year old infant, her somatic maturation has pursued a course similar to that of her brother and shows an astonishingly close correlation with her chronologic age. An experiment with testosterone propionate, which is being carried out in collaboration with Dr. Sydney Werner, gives indication of resulting in accelerated gain of height and weight.

Four of the midgets are brothers and sisters, of German parents. Their ages vary from 26 to 41 years, their heights from 114 to 131 cm. (46 to 52 inches) and their weights from 24 to 29 Kg. (53 to 64 pounds) Although their intelligence is mature, all show conspicuous skeletal and somatic retardation. In no case has epiphysial union or sexual ripening taken place. Three have alleged that they continued to grow at a slow rate until recently; one asserted that she is still growing at the rate of 1 cm. (0.4 inch) per annum.

The seventh midget, whom Dr. W. C. Schonfeld brought to our notice, is of particular interest in that he remained extremely small during childhood and at 16 years of age was only 112 cm. (45 inches) tall. For three years he was affiliated with a troupe of midgets and his stature appeared stationary. In his seventeenth year genital growth commenced, and between the ages of 19 and 21 years he advanced 43 cm. (17 inches) in height, thereby "growing himself out of a job." Examination at the age of 35 years revealed that he was 153 cm. (61 inches) tall, weighed 48 Kg. (105 pounds) and was normal in all aspects of function.

Our studies of these midgets have led to no conclusions concerning the pathogenesis of their defect of growth. Through the cooperation of Mrs. G. A. Graham, Dr. C. B. Davenport and Dr. C. W. Dupertuis we have obtained extensive anthropometric data relating to the subjects of this report. Our intent to compare these data with similar measurements in cases of verified pituitary dwarfism has been defeated by the lack of comparable clinical observations in the numerous cases in which the diagnosis was proved by surgical operation and in the less common cases in which the diagnosis was confirmed by autopsy. The unpredictable peculiarities of growth in our cases emphasizes the necessity of critical reserve in interpreting the consequences of the treatment of human dwarfism with endocrine preparations.

DISCUSSION

DR. LAWSON WILKINS, Baltimore: In nearly all respects I agree with the observations and conclusions of Dr. McCune and his associates, and I strongly commend his modesty about drawing any positive conclusions in regard to the cause of dwarfism in such cases as those presented.

Dr. McCune pointed out in his talk the fundamental need of differentiating between growth and development. His observations have coincided largely with those which my associates and I have made in that for the most part osseous development and sexual development coincide to a certain extent. His patients who achieved sexual maturity were those who had fairly normal osseous development.

We have been carrying out observations on about 40 different dwarfs in the course of the last six years and have records for periods of ten or twelve years in many instances. Some of these dwarfs have an osseous development which is normal or parallels the normal. In other cases there is a lag in the rate of bone development as great as in cases of marked hypothyroidism.

We are much interested in knowing just how close is the coincidence between the sexual development and the osseous development, because when we see such dwarfed children at an early age we should like to be able to predict which ones are going to mature sexually and which are going to remain infantile indefinitely.

Dr. McCune touched on the effect of androgens in the treatment of such patients. We have treated a few patients, as has been done in various parts of this country,

and we have seen striking stimulation of growth produced by administration of androgen. We have used methyl testosterone. Estrogens, such as stilbestrol, apparently do not accelerate growth. We have made balance studies and have found that androgens cause marked retention of nitrogen, while stilbestrol does not.

We are now treating 2 sexually infantile female dwarfs with a mixture of stilbestrol and methyl testosterone and so far have been able to avoid virilizing effects and have caused acceleration of growth. The dose they are receiving are 1 mg. of stilbestrol and 25 mg. of methyl testosterone.

Hormonal therapy offers possibilities, and I feel that the danger of premature fusion of the epiphyses, which has been pointed out in the past and which has kept physicians from attempting to cause an adolescent spurt of growth by means of androgens, is probably overexaggerated. Normal adolescents have a period of perhaps five years of rapid growth before there is complete fusion of the epiphyses.

DR. DONOVAN J. MCCUNE, New York: I have nothing to add except to ask Dr. Wilkins what has been the maximum amount of growth which he has procured with methyl testosterone.

DR. LAWSON WILKINS, Baltimore: Our work has gone on for only five months and with few patients; they have not grown over 2 inches (5 cm.) during that time, but we have a control in that they previously had been treated intensively with preparations containing so-called growth-stimulating principles, thyroid and other substances, with no effects. They now show satisfactory effects, and we have satisfactory biochemical evidences of growth.

Congenital Deformities Occurring in the Offspring of Rats Reared on Deficient Diets. DR. JOSEF WARKANY and DR. ROSE C. NELSON (by invitation), Cincinnati.

When female albino rats of the Sprague-Dawley strain were reared on the Steenbock and Black diet 2965 supplemented with viosterol in oil, congenital abnormalities were observed in about one third of their offspring. The males used in these breeding experiments were on an adequate stock diet. Some of the congenital malformations of the offspring could be seen on external inspection. The mandible was often short and the tongue protruded. Various deformities of the extremities could be observed, particularly syndactylism. A better appraisal of the skeleton could be gained after the newborn rats were cleared by the Schultze-Dawson method. The cleared specimens showed shortening or absence of the tibia, fibula, radius and ulna; shortening of the mandible; fusion of the ribs, and fusion of the centers of ossification of the sternum. Other bones were less frequently affected. In a few cases gross abnormalities of the soft tissues could be seen externally. Thus, thinning of the abdominal wall in the midline with or without protrusion of abdominal organs could be observed. Reduction in size of the genital tubercle and abnormalities of the eyes occurred. The histologic examination of abnormal long bones revealed persistence of cartilage in places where it should have been supplanted by bone. It is not known why the normal process of ossification is disturbed in these animals. However, the fact that the addition of 2 per cent of dried pig liver to the deficient diet of the mother will prevent the abnormalities described points to a nutritional factor necessary for normal ossification. This factor is apparently contained in large amounts in liver, and experiments are under way which may lead to its detection.

DISCUSSION

DR. HENRY J. GERSTENBERGER, Cleveland: In 1935 Mr. W. O. Frohing, who was interested in carotene, came to me with a request to photograph the puppy with the double harelip which you see in this lantern slide. (Slide) It was born of a mother who was fed a vitamin A–deficient diet, a fact which was of interest in view of the observations made by Hale and others at the Texas Agricultural Experiment Station on gilts which had been fed vitamin A–deficient diets and whose young presented various congenital malformations, principally involving the eyes but also including such abnormalities as harelip and cleft palate.

An experience which I had during the first half of 1940 with a premature infant who weighed 1,600 Gm. at birth and later presented the classic picture of congenital atresia in the biliary tract may also be of interest in this connection. (Slide) This lantern slide presents the pertinent data, which show that after large doses of vitamin A (six doses of 50,000 international units daily) in the form of halibut liver oil had been given for twenty-one days an improvement began which ended with complete disappearance of the symptoms; that is, the vitamin A level in the blood became more nearly normal, the icteric index fell to normal and the stools were no longer alcoholic. During the month preceding this form of therapy 445,000 international units of synthetic vitamin A had been given perorally and subcutaneously during a period of five days without any demonstrable improvement in the biliary picture, although the severe pyuria, which was resistant to treatment and for which the vitamin A therapy was really started, had been decidedly improved. On two subsequent days a total of 700,000 international units of vitamin A was given in the form of halibut liver oil, also without any improvement in the biliary picture. This was followed by the daily administration for twenty-one days of carotene in oil in large doses (40 drops before each of six feedings). No clinical improvement followed this form of therapy, and the diapers continued to show the vivid orange-yellow oily staining which one also sees in the cases of infants with cystic fibrosis of the pancreas. I feel that this simple test of administering carotene in oil perorally is a reliable, practical method of learning whether malnourished, nonicteric young infants do or do not have pancreatic disease of this kind.

The remarkable disappearance of the biliary symptoms in this case, in other words, was a fortunate, accidental development which followed intensive vitamin A therapy originally given to influence a severe pyelitis on the assumption that the infection might be secondary to a vitamin A deficiency.

I am aware that improvements such as I have just described have been reported before; however, in both of the 2 cases which I found in the literature the patient was a premature infant, as was my patient, and I am wondering whether prematurity may not be a factor in making intensive vitamin A therapy effective. All physicians have seen patients with congenital atresia of the biliary tract who showed additional congenital malformations, and it may very well be that in many cases the abnormalities have a pathogenesis similar to that operating in the case of the offspring of the gilts described by Hale. In recent years articles have appeared, particularly in the German literature, dealing with the nutritional causes of cleft palate and harelip. Dentists and surgeons seem to have been most interested in such discussions.

The work which Dr. Warkany reported this evening is also highly suggestive that many congenital malformations may be due, at least in part, to a defect in the diet or possibly to the inability of the fetus, at a certain period of its development, for some reason or other, to utilize the material available to it in the blood of the mother.

Intoxication Versus Deficiency in Experimental Dietary Conditions. Dr. Paul Gyorgy, Cleveland.

Classic deficiency diseases, such as scurvy or beriberi, are due to lack of a specific food constituent and can be produced by withholding the specific vitamin from the diet of man or animal. Recently, several experimental dietary diseases have been studied in which deficiency of vitamin-like substances is closely interrelated with apparently "toxic" dietary factors. Both conditions, deficiency and "toxic" factor, have to be present simultaneously in order for the specific disease to be produced.

In pathologic manifestations of this kind the question of "deficiency versus intoxication" is often not so easy to answer, although from one point of view such conditions can always be looked on as deficiency diseases of a particular type. This conclusion is borne out by analysis of three selected examples: (1) egg white injury versus deficiency of biotin; (2) dietary liver injury (necrosis, cirrhosis);

cystine intoxication versus deficiency of choline plus cystine, and (3) necrosis, cirrhosis and carcinoma of the liver in rats following ingestion of paradimethylaminoazobenzene ("butter yellow"); "butter yellow" intoxication versus deficiency of choline plus cystine plus other undetermined factor(s).

Third Session

Friday Morning, May 23

Tuberculosis in Adolescence. Dr. Edith M. Lincoln (by invitation), New York.

In the majority of cases in adolescence the lesion of primary tuberculosis cannot be visualized in the roentgenogram, and the mortality from the primary phase of the disease is small. When the primary complex is larger and can be seen on the roentgenogram, the mortality may be much higher; it was 25 per cent in a group of patients seen in the chest clinic of the children's medical service of Bellevue Hospital. The same relation of the extent of the disease to the mortality was seen in the cases of infants, in which the mortality rate was six times greater when the complex was observed roentgenographically than when the reaction to tuberculin tests was positive and the roentgenogram normal. The chief form of the disease in adolescence is tertiary, or chronic pulmonary, tuberculosis. This usually develops at or near maturity regardless of the age of the child when first infected. In follow-up examinations of the surviving patients of a group of 1,000 with primary tuberculosis seen in the children's chest clinic, it was found that so far tertiary pulmonary tuberculosis has developed in 6 per cent, of which 70 per cent are girls, with an average age of 13 years. The relation of sexual maturity to the development of tertiary tuberculosis is not understood, but it is known that the peak of the mortality from tuberculosis occurs much earlier in girls than in boys. No means of preventing tuberculosis in adolescence will be available until this problem has been solved.

The best method of finding cases of tertiary pulmonary tuberculosis is to make follow-up roentgen examinations of children who have had primary tuberculosis and of adolescents who display positive reactions to tuberculin tests, regardless of whether the primary lesion is visualized on the roentgenogram. The mortality in the group of cases found by this method in the children's chest clinic was 25 per cent, as compared with a mortality rate of over 50 per cent in groups of cases of chronic pulmonary tuberculosis not found by this method.

DISCUSSION

Dr. Charles Hendee Smith, New York: It is perhaps peculiarly fitting that Dr. Lincoln should present this report this year, because it is the twenty-fifth anniversary of the establishment of the special clinics for diseases of the heart and chest in children in Bellevue Hospital. Obviously, only by continuous and concentrated observation on groups of children is it possible to get the kind of information that Dr. Lincoln has collected. The patient with disease of the chest in a general pediatric clinic gets amateur attention, one might say. I believe strongly, as I did twenty-five years ago, that the way to get better results with these large groups is by superimposing experience instead of spreading it out thin.

Some years ago it became evident that poor children with diseases of the heart and chest were being lost from observation in the time between the pediatric age and the age when there was development of later trouble and they appeared in the adult clinic. That interval is the critical time. Some six or seven years ago the clinics for adolescents were established, with the consent of the services for adults because they felt they were not seeing such patients early enough.

These clinics, which are held in the early evening once a week, for patients with diseases of the heart or chest, have added a great deal to the physicians' ability to care for these patients.

These patients are children, really. The mere advent of puberty does not make them adults. Their problems of hygiene and their behavior problems are still those of children. They are fond of their physicians in the children's clinic but do not like to go to an adult clinic; in fact, they will not attend one, but will keep coming back to the children's clinic, in which they have grown up. I do not know how long they come on the average, but some of them, I know, have been followed up for twenty years or more.

The physician who works with adults often is not interested in child hygiene, or in any hygiene for that matter. The fact that such children as those I am discussing are under the stress and strain of adolescent life is forgotten. They need much rest and reasonable food and all the other things which go to make up a proper mode of life, and they need it at this critical age even more than they did as children. The mortality rate for tuberculosis is not small, as Dr. Lincoln has said. The only way it can be reduced is by keeping the children under continuous observation through the critical period. In some tuberculosis projects dealing with children no pediatrician has been included. The persons in charge did not think it worth while to treat or even to examine the patients at all; they merely sat and reviewed roentgenograms.

The relation of primary tuberculosis to the later apical lesion has always been puzzling and interesting. I once was on a committee in New York which met for two hours every week all winter, and the main points of discussion were whether adult tuberculosis was a reinfection or a recrudescence. At the end of the year the members of the committee went out the same door they went in. But there is constantly increasing evidence that the so-called Simon tubercles (hematogenous seedings) in the apexes of young subjects are the source of adult tuberculosis. As Dr. Lincoln said, in children who have been separated from their source of infection apical disease may still develop. Simon tubercles are not easy to demonstrate in all cases, but they are easily seen when calcified. The person who says they are not there unless they are calcified and visible forgets that tuberculosis can persist or resolve and disappear without calcification, in which case the small seedings will be invisible. It seems to me that such hematogenous foci offer the best explanation for recrudescence—a certain explanation in many cases and a probable one in most cases.

I hope that tuberculosis in adolescence will be followed up by pediatricians more and more throughout the country.

DR. CHARLES G. KERLEY, New York: Dr. Lincoln will remember that a few years ago she looked over the roentgenograms of 4 babies in which were signs of consolidation in the lung without any evidence of illness; bronchial breathing and bronchial voice had been found on routine examination.

The puzzling part was that, with evidence and signs that beyond dispute related to the complex, no positive reactions to the Mantoux, Vollmer or von Pirquet tests were obtained. These children have been followed for seven or eight years, and the signs have all cleared, as shown roentgenographically and by auscultation. The process in the lung has cleared entirely, in all cases, without any evidence of calcification. The children made a complete recovery, and had not careful examinations been made of the chest it would never have been known that they had trouble of this sort.

Interpretation of roentgenograms of the lungs in infancy and in childhood is most difficult; roentgenologists supposedly expert sometimes differ widely in their conclusions.

DR. HORTON R. CASPARIS, Nashville, Tenn.: I am a little confused about what is meant by primary tuberculosis. Does it mean manifest or symptomatic tuberculosis or tuberculous infection with changes in the roentgenogram that can be attributed to that infection?

I noticed in your talk, Dr. Lincoln, that you omitted mention of secondary tuberculosis and skipped over to the tertiary type. Just where does primary tuberculosis end and secondary or tertiary tuberculosis begin?

DR. BÉLA SCHICK, New York: Dr. Lincoln spoke of the need for wards and clinics for adolescents. I agree with her fully. For many years I have fought for them, because I feel that if nothing is done about them the pediatrician will lose contact with the adolescent group.

I have the opportunity of keeping children in the Sea View Hospital from the beginning of their tuberculosis, through adolescence and up to the age of about 16 or 17 years, when I lose them. I should like to keep them even longer, for continuous observation helps in the classification and increases the knowledge of tuberculous infections.

As far as the frequency of the primary infection type is concerned, I should like to point out, as I did two or three years ago, that with the decreasing number of positive reactions to tuberculin in childhood one must expect more primary infections with tuberculosis during adolescence and in adult life. My associates and I have found that at the age of 14 years only about 35 per cent of the reactions to tuberculin are positive. Dr. Charles Hendee Smith found a similar incidence. I saw in the last fourteen days 3 adult patients in Mount Sinai Hospital with the characteristic picture of the primary infection type of tuberculosis.

I should also like to point out the importance of foci in the subclavicular region. Recently, Wallgren published an excellent article in which he discussed whether pediatricians should be satisfied because there is less tuberculous infection during childhood. He expressed the belief, and I agree with him, that it is preferable to have the primary tuberculous infections during childhood (after 5 years of age) and adolescence, at a time when the subject can have bed rest and all other necessary treatment, as he does not have to support a family or face the danger of losing his position.

I think that the American Pediatric Society should do something about the problem of caring for adolescent patients, because the pediatrician will be pushed aside by the specialists in tuberculosis, endocrine disorders, diabetes, and so on, and finally will be left with only the infant and the smaller child in his charge.

DR. EDITH M. LINCOLN, New York: In answer to Dr. Kerley's question about the cases in which there is a negative reaction to tuberculin but a lesion shows up in the roentgenogram, I, of course, think the burden of proof is on any one who makes the diagnosis of primary tuberculosis or any form of tuberculosis in the case of any child who is not moribund and displays a negative reaction to the tuberculin test.

There is no doubt that such cases do occur. Dr. Milton Levine reported some at the meeting of the American Academy of Pediatrics, and reports were published in the AMERICAN JOURNAL OF DISEASES OF CHILDREN. Also, my associates and I have seen 3 or 4 instances among several thousand cases of tuberculosis at Bellevue Hospital.

I believe that Dr. Kerley's comment on the low rate or absence of mortality and the absence of calcification bears out the point which I was trying to make, that dosage has a great deal to do with the mortality from tuberculosis. Very low dosage explains the low mortality and the low incidence of calcification in some cases.

In answer to Dr. Casparis' question, it is difficult to define primary tuberculosis. By primary tuberculosis I mean the infection which occurs when a subject for the first time becomes infected with tubercle bacilli. This may consist simply of a few tubercles just under the pleura in the lung which may never be visible in the roentgenogram and may never go on to calcification, or the dose of tubercle bacilli may be so massive that a progressive primary lesion results, which spreads locally and hematogenously. But whatever the amount of infection,

it is known that there usually is a change in the body reaction some time between three and six weeks after this infection which causes a positive reaction to the tuberculin test, and I believe one should not try to differentiate between tuberculous infection and primary tuberculous disease, because every first infection is an instance of primary tuberculosis.

The secondary stage I passed over because I was trying to concentrate on chronic pulmonary tuberculosis. Of course, it usually implies the lymphohematogenous spread and the local spread by lymphatic and bronchiogenic means. The first and second stages constitute tuberculosis at the portal of entry, or the early stages of tuberculosis.

Tertiary tuberculosis is not an ideal term. It has been employed largely by Wallgren, but all the other terms are equally bad. Reinfection tuberculosis implies that the infection is exogenous. Adult tuberculosis implies that it occurs only in adults. Chronic pulmonary tuberculosis is objected to because in a great many cases the disease is acute, not chronic. I still think, however, that chronic pulmonary tuberculosis, which is largely used by the workers in the National Tuberculosis Association, is probably the best term to use.

I did not mean, Dr. Schick, to gloss over the importance of the subclavicular lesion, but most of those which are seen in the young adolescent group are secondary to apical lesions, and the primary subclavicular lesions which appear in the absence of any previous lesion of chronic pulmonary tuberculosis occur, in my experience, in a slightly older age group.

"Streptococcosis" and "Streptococcic Fever." DR. PHILIP A. BEARG (by invitation), DR. PAUL L. BOISVERT (by invitation), DR. DANIEL C. DARROW, DR. GROVER F. POWERS and DR. JAMES D. TRASK, New Haven, Conn.

The terms "streptococcic fever" and "streptococcosis" have been coined by Dr. Darrow and Dr. Sinclair to describe some common features of infection with hemolytic streptococci. In this report streptococcosis will be used in much the same way as tuberculosis is used currently, that is, to denote that one organism is the etiologic agent in a variety of conditions of considerable clinical and anatomic dissimilarity. For example, in a tuberculous family one might find meningitis, scrofula, tabes mesenterica, disease of the hip and phthisis. In the same way, in a family with scarlet fever one might also observe erysipelas, cervical adenitis, follicular tonsillitis and all the septic features of streptococcic infection and their nonsuppurative sequelae, such as hemorrhagic nephritis, erythema nodosa and rheumatic heart disease.

The experimental work of this report consists in epidemiologic visits made by Dr. Boisvert and Dr. Bearg in the homes of 40 families with scarlatina which had 250 members and in the homes of 30 control families with pertussis which had 190 members. Bacteriologic and clinical observations were made on all subjects. The strains of hemolytic streptococci recovered from the families with scarlatina were typed. Two chief types were found: Griffith's type 1 and type 3. However, in any one familial outbreak a single type was usually found. The diseases associated with one type were diverse, according to current usage. Such conditions as erysipelas, otitis media, cervical adenitis, scarlet fever and acute follicular tonsillitis were caused by one type of Streptococcus. Accordingly, these different conditions were taken to be examples of one disease, streptococcosis, the clinical manifestations of which were closely related to the age of the patient. When the clinical data were analyzed, it was seen that about 78 per cent of the children under 15 years of age had had streptococcic illnesses and 37 per cent of the children over 15 and the adults had had similar disorders. Scarlet fever was commonest in the group aged 3 to 15 years, streptococcic pharyngitis and acute follicular tonsillitis in the older age groups and cervical adenitis without a rash (streptococcic fever) in the group aged 1 to 3 years. Hemolytic streptococci were recovered from 90 per cent of the sick and from 15 per cent of the healthy familial contacts.

In the 30 control families the carrier rate was 14 per cent. The carrier rate among subjects below 6 years of age was 9 per cent and among those older than 6 years 17 per cent. No carriers were found in 18 families, and in the remaining 12 the carrier rate was 33 per cent, but for each carrier relatively few colonies were found in the plates made of material from the throat.

To summarize, clinical and bacteriologic data collected in familial epidemics indicate that streptococcosis and streptococcic fever may be employed as appropriate terms to describe infection with hemolytic streptococci in man.

DISCUSSION

DR. PAUL L. BOISVERT, New Haven, Conn.: Cultures are valuable in corroborating the clinical diagnosis of streptococcic disease and in identifying those forms of streptococcosis which are less obvious.

Cultures of material from the throat are the most widely used because the primary lesion in the large majority of streptococcic infections is in the throat. My associates and I obtain material for cultures by swabbing both the tonsils and the posterior wall of the pharynx with a cotton-tipped applicator.

(Slide) Slide 1 is a photograph of a culture of material from the throat of a child with scarlet fever. The hemolytic organisms are streptococci. In our experience, cultures of material from the throat are positive for streptococci for 91 per cent of the children examined during the first few days of a streptococcic illness. If a repeat culture is made for those children whose first culture was negative for streptococci, the total incidence of positive cultures is 96 per cent. The so-called carrier rate is 6 per cent among children.

Cultures of material from the nose have advantages which deserve special consideration. Such a culture for a well child will yield a few colonies of staphylococci and diphtheroids. This is in contrast to the normal flora of the throat, which is complicated and contains organisms which resemble hemolytic streptococci in appearance of the colony. In cultures of material from the nose for sick children, hemolytic streptococci are frequently found. This we take to be a sign of bacterial activity. The presence of these organisms, often in large numbers, makes a striking picture.

(Slide) Slide 2 is a photograph of a culture of material from the nose of a child with scarlet fever. Hemolytic streptococci are present in almost pure culture.

Material for culture is obtained from the nose by tilting the tip of the nose upward and gently inserting a cotton-tipped applicator backward along the floor of the nostril until the nasopharynx is felt. Technically, material from the nose is more satisfactory for culture than material from the throat, because the region from which it is obtained is definite and there is no danger of interference with growth of the organism through contamination with saliva.

Cultures of material from the nose are highly specific. It is our impression that the presence of hemolytic streptococci in the nose indicates bacterial spread and disease and is analogous to a positive blood culture, which denotes major bacterial activity.

Serologic tests furnish an additional means of diagnosis. We use the fibrinolysin test, which is inexpensive and simple. Hemolytic streptococci will rapidly dissolve the plasma clots of normal subjects, and a positive reaction to the test depends on the presence in the patient's blood of a substance which makes the clot resistant to liquefaction.

(Slide) Slide 3 shows at the left the type of clot which forms after the patient's plasma, a stock culture of hemolytic streptococcus and calcium chloride are mixed. The tube is inverted to show that the clot is solid. The middle tube contains a dissolved clot. The reaction to the test in this case was read as negative, because complete liquefaction occurred within one hour. One hour is the upper limit of normal. The clot in the tube to the right is still solid at the end of twenty-four hours, which indicates a 4 plus reaction to the test.

(Slide) Slide 4 shows the clinical course and the results of fibrinolysin tests in the case of a 3 year old child with scarlet fever. He was admitted on the second day of the disease, with a temperature of 104.5 F. Tests gave negative results early in the illness, and then the reactions became increasingly positive. Data are not shown on the slide, but in this case the positive reactions persisted for two weeks. The reaction to the test is positive for about 85 per cent of children with a streptococcic infection, at a time when, in the absence of suppuration, it may be difficult to recover the streptococcus by cultural methods.

The test is not entirely specific. Positive reactions may be encountered in cases of such diseases as pneumococcic pneumonia. Such exceptions, which occur only early in a highly febrile illness, prevent one from making a definite diagnosis of streptococcic disease purely on the basis of a positive reaction to the test. However, a positive reaction appearing during the course of an illness or a positive reaction to a second test a few days later makes the diagnosis clear.

DR. GROVER F. POWERS, New Haven, Conn.: There is so much talk on the subject of streptococci that I thought it might be well to find out something about the incidence of the organism. Consequently, Dr. Boisvert and I studied the records of the children who were admitted to the inpatient service of the children's clinic of the New Haven Hospital during a period of six years. The patients admitted ranged in age from newborn infants to children who had passed their sixteenth birthday. The children admitted during 1934, 1935 and 1936 constituted group 1. We skipped 1937, for that was the year in which sulfanilamide was introduced; then we took data for 1938, 1939 and 1940 (group 2).

(Slide) It will be seen from the slide that there are about 2,000 children in the first group and about 2,800 in the second group. The proportion of children for whom cultures of material from the nose and throat were made was about 91 to 96 per cent, and of these, about 75 per cent did not have hemolytic streptococci in the nose or throat and about 25 per cent did. Of the children with cultures positive for hemolytic streptococci, 1 in 7, or 15 per cent, actually had unmistakable streptococcic disease. That means that about 10 per cent of the children might be called carriers: either healthy carriers or sick carriers, or, as I prefer to call them, patients with latent streptococcosis.

All of these children were patients in the public wards, and I am well aware that with a different type of pediatric setup the data might not be the same.

(Slide) The next slide shows totaled data for the three years before and the three years after the advent of sulfanilamide for streptococcic fever, tonsillitis and laryngitis. Contrary to what Dr. Park and I used to think, in New Haven, Conn., laryngitis seems to be infrequently caused by the streptococcus; it is usually caused by the pneumococcus or the influenza bacillus, or in the absence of those pathogens, possibly by a virus.

When we brought together the data for the three years for each group, we found that streptococcic fever among children under 3 years of age is six times as common as scarlet fever and that among children from 3 to 11 years of age it is twice as common as scarlet fever, showing that on the basis of numerical incidence the important form of streptococcic infection is streptococcic fever.

It will be noted that there were a great many cases of suppurative otitis media in the second group, but the incidence of mastoiditis which required operation in the second group was very low; this undoubtedly is due to the advent of sulfanilamide and is, I think, one of the outstanding features in the study. The same is true of meningitis.

There were 19 cases of suppurative retropharyngeal abscess and tonsillar abscess in the first group and only 5 in the second group; I have no explanation for this difference in incidence. It could hardly be due to sulfanilamide, for most of the children were admitted with the condition before the employment of sulfanilamide.

It will be noted that in 1940 there were 5 patients with streptococcic vaginitis. Actually, in that year there were 10, but 5 of them were seen in private practice

or in the dispensary, and therefore data for them were not in the hospital records. Undoubtedly we have missed that diagnosis previously. We feel the condition is a definite entity which we have just learned to recognize. The 10 children who had it were from 13 months to 13 years of age. A pure culture of the organism was obtained. In 2 cases there was perineal erysipelas; in half of the cases the organism was found in the throat; the onset was stormy, and there were dysuria and vaginal discharge.

(Slide) The last slide illustrates something of our concept of the nosology of streptococcosis in children. You notice here the term streptococcic fever, introduced by Dr. David C. Darrow. I don't know whether Dr. Darrow would quite recognize his child now; his term has gone through childhood and adolescence since he first suggested it. The characteristics of the disease are that it occurs in children under 3 years of age, that the streptococcus is the predominating pathogen in the respiratory tract and that there are associated pharyngitis, cervical adenitis and otitis media; the patient is miserable, he has anemia and has lost his appetite; the disease usually lasts six weeks, and the patient is not his usual self for a much longer period.

After 3 years of age the disease may occur, but the salient features are different. There is a stormy onset. The pharyngitis lasts a much shorter time. There may be follicular tonsillitis. The duration is usually less than a week.

In our classification we naturally had cases of clinical streptococcosis, in which the bacteriologic data confirmed the diagnosis; some forms of the disease, namely, scarlet fever and erysipelas, could be recognized as streptococcosis without bacteriologic data. In some cases of streptococcosis the diagnosis was established by bacterial examination of material from the suppurative lesion, as, for example, in cases of suppurative adenitis, otitis media, empyema, peritonitis or meningitis, or by examining the blood in cases of bacteremia. Such lesions may be secondary to streptococcic fever or scarlet fever.

In the cases of the group of subjects whom some writers might call carriers the bacteria are spoken of as secondary invaders. In such cases I speak of the condition as latent streptococcosis, and I think that at present this is the most important group for study.

In addition, there are the group with acute glomerulonephritis and the controversial group with rheumatic fever.

Dr. John D. Lyttle, New York: I should like to ask the authors if they think one should isolate children with this disease.

Dr. William L. Bradford, Rochester, N. Y.: I should think that persons interested in public health administration would find considerable interest in the practical facts implied by this new terminology. In my community, if a child with a streptococcic infection of the throat exhibits a rash, he is isolated for twenty-one days; if a rash does not develop, he is isolated for as long a period as is required for him to feel well.

From Dr. Boisvert's discussion I inferred that a culture of material from the nose which was positive for streptococci indicated an extension of the primary infection of the throat. Perhaps the occurrence of sinal infection as a complication would support this concept clinically. I should like to ask Dr. Boisvert if simultaneous cultures of material from the nose and throat were made and if they indicated whether the infection began in the nasopharynx or in the throat.

Dr. John A. Bigler, Highland Park, Ill.: A few years ago my associates and I took material from the nose and throat for culture from all the children admitted to the Children's Memorial Hospital, Chicago, over a period of three years. The material for culture was obtained before they were actually patients in the wards. We found about the same proportion of cultures positive for hemolytic streptococci, that is, about 25 per cent, as Dr. Powers has reported. The patients included children who had infections of the upper respiratory tract, and so forth.

Of the children who were admitted for tonsillectomy only, about 15 to 17 per cent had cultures positive for streptococci, although their throats appeared normal. So a great many children do have streptococci present in the nose and throat at all times.

I am reluctant to bring up the question of scarlet fever in this discussion, but I have been bothered a great deal about the relation between so-called scarlet fever, cultures of material from the nose and throat and reactions to the Dick test. In performing Dick tests on children with a history of scarlet fever (many of them had been in contagious disease hospitals; so their physicians, at least, thought they had scarlet fever) we found that of the children who contracted the disease between the first and the third year of life 50 per cent later had a positive reaction to the Dick test. Of those who had the disease after the third year of life, only 20 per cent had a positive reaction to the Dick test one to five years later. When, in cases of streptococcic disease, with or without a rash, can one make a diagnosis of scarlet fever? All physicians have seen in families with streptococcic disease members who had a rash, others who did not, and still others who did not have a rash yet who exhibited desquamation afterward. What about quarantine in cases of streptococcic disease? I should also like to ask whether Dick tests were done on any of the patients with hemolytic streptococcic disease.

Dr. Béla Schick, New York: I am glad that Dr. Trask resurrected my paper of 1905. First, regarding the nomenclature, I prefer the name streptococcic disease. When Pirquet and I wrote on serum disease we had the same difficulty with terms. For a while we called it serum fever; later we changed the name to serum disease. If one calls it fever, only one symptom is emphasized, whereas if the name streptococcic disease is used all of the symptoms are included.

The observations on postscarlatinal fever interest me from the point of view of sensitization. I had the idea that the primary part of the scarlet fever process was due to the primary toxin and that in the third week allergic reactions occurred. It was interesting to learn that the primary complex of scarlet fever leads to sensitization. This sensitization in scarlet fever appears in about three weeks. Postscarlatinal nephritis is thus a sensitization phenomenon.

There are frequently a second and a third flare-up of the original process. In diphtheria the development of sensitivity to certain toxins leads to pseudoreactions.

I should like to ask Dr. Trask whether in his cases he observed flare-ups of the original streptococcic disease.

Dr. Charles G. Kerley, New York: It has been my observation that in infections of the upper respiratory tract the predominating bacteria vary a good deal from year to year. In the last two or three years the streptococcus had predominated in my cases and in those of my associates.

Dr. Hugh McCulloch, St. Louis: I wish Dr. Powers would remove the question mark after rheumatic fever in his last slide, category F, for thirty years from now, when that slide is shown again, it may still be there.

Dr. James D. Trask, New Haven, Conn.: Some of the questions may perhaps be answered by the further epidemiologic use of Mrs. Lancefield's methods of identifying streptococci. In particular, I hope that her methods may help to answer Dr. Lyttle's question as to the infectiousness of streptococci. Dr. A. R. Dochez has long been looking for a test of infectiousness. Recently his colleague, Dr. A. F. Coburn, reported (*J. Exper. Med.* **73**:551 [April] 1941) on some special attributes of infectious strains of streptococci and stated that infants were more apt to communicate infection than sick nurses or physicians. The communicability of streptococci has been studied indirectly by those who have concerned themselves with cases of "return" scarlet fever. Among students of this problem Dr. C. V. Chapin, of Providence, R. I., and Dr. John E. Gordon, formerly of

Detroit, should be mentioned. Dr. Gordon concluded that communicability had to do with the age of the convalescent and with the season of the year. Thus, he found that the highest number of "return" infections occurred among convalescents under 5 years of age in the winter and the lowest among those over 15 years of age in the summer.

To answer Dr. Bigler, we did not perform Dick tests in the series described. I might add that we believe that there is more than one scarlatinal toxin.

To answer Dr. Schick, we did see instances of a relapsing course during streptococcic fever.

With regard to cultures of material from the nose, I should like to add that the presence of hemolytic streptococci is closely restricted to cultures for subjects who have recently been or are sick with streptococcic disease. In this sense the observation is a sign of streptococcic activity in much the same way, but to a lesser degree, that a positive blood culture is a sign of streptococcic activity.

Cultures of Material from the Nasopharynx of Patients with Pertussis.

Dr. W. L. Bradford and Dr. Ann Morris Brooks (by invitation), Rochester, N. Y.

The present report describes the results of 352 cultures of material from the nasopharynx and 159 cough plate cultures made in 216 cases of clinical pertussis.

The technic of obtaining the material from the nasopharynx for culture is as follows: A swab consisting of a small bit of cotton tightly wound about the end of a small, flexible copper wire is passed through the nares until it touches the posterior pharyngeal wall. The surface of a plate of freshly prepared Bordet's medium is then inoculated with the material in the swab by streaking finely with a long flexible platinum loop. After incubation for seventy-two hours at 35 C., the plate is inspected for colonies of Haemophilus pertussis. The cough plate culture is done in the usual manner.

In a series of 98 cultures positive for H. pertussis which were made simultaneously for 88 patients the results were as follows:

	Infants Under 3 Years	Children Over 3 Years	Total No. of Patients
Both cultures positive	20	17	37
Culture of material from nose positive, cough plate negative	33	14	47
Culture of material from nose negative, cough plate positive	2	12	14
	55	43	98

The results obtained indicate that, in this study, the method of using material from the nasopharynx for culture is definitely superior to the cough plate method, particularly in the case of infants.

DISCUSSION

Dr. James D. Trask, New Haven, Conn.: My associates and I can corroborate Dr. Bradford's observations on the ease with which positive cultures of material from the nose are obtained from infants with pertussis. He suggested that I might have had something to do with the popularizing of such cultures, but credit really belongs to Mrs. Gordon Vogt, who, as Miss Agnes Beebe, worked as a bacteriologist at Yale University from 1927 to 1936. She kept telling me that one often got pure cultures of pneumococci, influenza bacilli and other pathogens from the nose. I passed this information by year after year, until Dr. Webster told me the same thing, and then we began to put it to practical use.

Spot Maps for Bacillary Dysentery and for Acute Epidemic Poliomyelitis. Dr. George M. Lyon, Huntington, W. Va., and Dr. Albert M. Price (by invitation), Charleston, W. Va.

The distribution of the child population in Huntington, W. Va., is shown in a copy of a spot map which was prepared by the board of education of Cabell County, in 1937.

The distribution of cases of measles reported to the department of health of Huntington during March and April 1941 is shown in a second spot map. The distributions of the cases of measles and the school population are very similar. Particular attention is drawn to the fact that the central, heavily populated and heavily built-up sections of the city are visited to the same degree as the outlying areas. Infections spread in the main by discharges from the respiratory tract tend to follow this pattern of distribution, and this has repeatedly been observed in epidemics of measles and influenza in the districts under consideration.

The distribution of cases of dysentery for the period 1921 to 1931 is shown in a spot map. In the districts known to have the poorest sanitary facilities, which favor the spread of intestinal diseases by flies and by other means, the highest incidence of acute bacillary dysentery is observed. Generally, but not invariably, these same districts had the most inadequate housing facilities, the most unfavorable economic status and the most unenlightened residents. The central districts, although heavily populated, regularly had few cases of dysentery. As compared with the distribution of measles this was worthy of note.

In 1937 Dr. Byrd Hunter drew our attention to the striking similarity between the distribution of cases of dysentery in the spot map, then in process of development, and the distribution of cases of poliomyelitis with paralysis in the epidemic of that year. The distribution of the 47 cases of paralytic poliomyelitis which occurred in 1937 is shown in a spot map.

In the epidemic of poliomyelitis of 1940, 45 cases of the paralytic type and 16 cases of the nonparalytic type were reported to the department of health of Huntington. The distribution of the cases is shown in a spot map. The pattern of distribution is the same as in 1937 and is very similar to that for dysentery in the spot map for 1921 to 1931.

In another spot map the places of residence of the patients with poliomyelitis for both epidemics are shown (there were 47 cases of the paralytic type in 1927 and 45 cases of the paralytic type and 16 cases of the nonparalytic type in 1940). The pattern of distribution observed in both the 1937 and the 1940 epidemics of poliomyelitis was similar to the distribution of bacillary dysentery for the years 1921 to 1931.

The distribution of the cases of poliomyelitis and of bacillary dysentery differed strikingly from the distribution of the cases of measles in that the children living in the heavily populated central part of the city were not attacked with the same frequency as were those living in the marginal areas, whereas those living in the outlying districts had an excessively high attack rate.

These observations suggest rather pointedly that the virus of poliomyelitis is not spread in the same manner as the virus of measles (through discharges from the respiratory tract). Furthermore, they suggest that the virus of poliomyelitis and the bacteria responsible for bacillary dysentery are spread in the same manner (discharges from the gastrointestinal tract, possibly by flies).

We believe that these implications are sufficiently strong, on their own merits, to encourage the development of investigations directed toward a study of the common housefly (Musca domestica) as a possible vector, which may lead to the actual demonstration of the importance of flies and of imperfectly protected stools and sewage as important factors in the epidemiology of acute poliomyelitis.

DISCUSSION

Dr. James D. Trask, New Haven, Conn.: Dr. Lyon enabled Dr. Paul and me to visit Huntington during the epidemic last fall. Dr. Paul and I have

written a good deal about the virus of poliomyelitis in stools and sewage. Some writers have implied that we think that the disease is transmitted directly by stools or sewage. Really, we are pretty open minded about the mode of transmission. As a matter of fact, it seems that the problem of infected sewage opens again the question of the relation of biting insects to poliomyelitis. The bar to the theory of transmission by a biting insect was that the virus was never found in the blood and no one could imagine how the insect could get hold of virus. But if the virus is distributed widely in the country anything can get hold of it.

We did not test flies from Huntington. We have tested flies from other communities with epidemics. The results have been negative, but the investigative attempts have not been good.

DR. LAWSON WILKINS, Baltimore: I should like to ask Dr. Lyon and Dr. Trask if this distribution, with the highest concentration of cases of poliomyelitis in the least densely populated community, could not be explained by the more complete immunization of the child population in the more thickly populated districts prior to the epidemic rather than by the assumption that the disease is spread by the gastrointestinal route, as is dysentery.

DR. JOHN A. TOOMEY, Cleveland: The authors' charts are suggestive. Clinically, infections of bacillary and other types of dysentery and of typhoid sometimes leave the patient with paralysis of a lower motor neuron type, as in poliomyelitis. Osler referred to such paralysis as "typhoid poliomyelitis." Moreover, in patients ill with diseases of the gastrointestinal tract, such as typhoid, typhus and bacillary dysentery, peripheral neuronopathy, with an increase in the number of lymphocytes in the spinal fluid and a positive reaction to the globulin test, sometimes develops, just as in poliomyelitis. It is sometimes extremely difficult to differentiate the conditions.

The charts represent a maximum amount of careful investigation. Of course, one might be tempted to conclude that since both diseases were of gastrointestinal origin the curves of incidence and the spot maps should coincide.

DR. GEORGE M. LYON, Huntington, W. Va.: I believe that there is not the same opportunity for group resistance to be developed naturally in a city of 80,000 people as in a large metropolitan area. In my opinion group immunity played no role in the paucity of cases of poliomyelitis and bacillary dysentery observed in the central population area.

After the epidemic of 1937 there were almost no cases of acute poliomyelitis in the city of Huntington until the summer of 1940, when a sizable epidemic occurred. The sporadic cases of poliomyelitis encountered in private practice in Huntington, since 1921, have almost all been those of patients brought into the city from rural districts for diagnosis and treatment.

I doubt very much whether group protection due to density of population and the development of group immunities therein has been a significant factor in the distribution of the cases described in our study.

Tetanus Antitoxin Levels in Infants Following Prophylaxis with Combined Alum-Precipitated Tetanus and Diphtheria Toxoids. DR. WILLIAM C. DEAMER (by invitation), DR. O. GEORGE BATES (by invitation) and DR. FRANCIS SCOTT SMYTH, San Francisco.

The question of the advisability of the routine use of combined tetanus and diphtheria toxoids suggested this study at the University of California Hospital. Over 500 infants have received three injections of the combined alum-precipitated toxoids in 1 cc. amounts. The interval between the first and the last injection was usually eight to ten weeks, occasionally longer. A sample of blood was taken two months or more after immunization for the determination of its tetanus antitoxin content, and a Schick test was done. Standard tetanus toxin was used in the antitoxin determinations, which were done on guinea pigs.

Analysis of the data for 134 patients whose immunization was completed in a period of eight to nine weeks shows great variation in the tetanus antitoxin response. The poorest response was shown by a value between 0.01 and 0.03 unit of antitoxin per cubic centimeter of serum. The best response was shown by a value between 3 and 10 units per cubic centimeter of serum. Only 4 infants had values of less than 0.1 unit of antitoxin. From these 4, blood was taken at intervals of ten, thirteen, twenty-five and forty-one weeks respectively after the last dose of toxoid. Two of these 4 patients were studied again after several months, and both were found to have more antitoxin then. Evidently they formed antitoxin slowly. The usual peak response appeared to occur eight to ten weeks after the last injection of toxoid. An analysis of data for 107 patients who were studied at that time showed a value of less than 0.1 unit per cubic centimeter in only 1 instance. It was also apparent that allowing an interval of over ten weeks between the first and the last injection led to a better response than when shorter intervals were used.

In interpreting these data it should be remembered that these responses are the initial ones. The program of tetanus prevention includes a "recall" injection of toxoid at the time of injury or possibly at regular intervals of several years. Reports indicate that such "recall" injections lead to marked and prompt formation of antitoxin within the incubation period of tetanus. Data from the present war suggest that even without the "recall" injections immunized soldiers are not likely to get tetanus.

Among our patients local reactions were not troublesome, although induration, tenderness and redness at the site of injection were frequently encountered. No abscess formation occurred in nearly 1,500 injections in infants. Sterile abscesses did form in 2 girls 7 years of age who were identical twins.

The proportion of negative reactions to Schick tests obtained was 96 per cent. There was no correlation of positive reactions to Schick tests and low tetanus antitoxin titers.

DISCUSSION

DR. FRANCIS SCOTT SMYTH, San Francisco: I think it is obvious that the title of this report might better be "Levels of Tetanus Antitoxin in Infants Following Injection of Combined Alum-Precipitated Tetanus and Diphtheria Toxoids," for we are not yet prepared to state that we have obtained the hoped-for prophylaxis.

I should like to emphasize some of the points Dr. Deamer has mentioned. First, I should say that tetanus has not been common in our service, but that it varies considerably in severity and that in cases of the more severe type the results of treatment are rather discouraging, despite massive doses of antitoxin and the use of avertin with amylene hydrate and other strong sedatives.

I think every one can recall failures of prophylaxis with a minimum dose of 1,500 units (U. S. P. H. S.) of antitoxin. Some physicians from St. Louis may recall that during the tornado at Murphysboro, Ill., despite the use of tetanus antitoxin for prophylaxis, there was a rather high mortality from tetanus.

In our own community the use of antitoxin for prophylaxis has almost a medicolegal status. One gives it for injuries incurred in the street; yet I saw an infant whose injury occurred in the garden (tumbling out of a high chair into a rose bed), where the roses had been fertilized recently with horse manure. The child was taken to a hospital, where careful suturing was done but no antitoxin administered, and ten days later had tetanus, which terminated fatally.

I have also had certain patients with known serum sensitivity whom I have warned in order to prevent possible needless use of antitoxin after a street injury. A case comes to mind in which the injury occurred from crushing the finger in the door of a new car and I had to take the responsibility of persuading the physician not to use antitoxin because of the patient's sensitivity.

It seems to me that it would be helpful to know more about the spore content of streets today as compared with, say, 1900. We are far from satisfied with the current accepted dosage and the status of prophylaxis with tetanus antitoxin.

As Dr. Deamer said, I, too, think there must be some factor other than antitoxin in the method of protection, but the report of cases other than 1 or 2 of otitis media, in which there was seemingly a latent infection with tetanus, and certainly some of those in South American cities, strongly suggest that there is no absolute proof of immunity to tetanus.

DR. WARREN R. SISSON, Boston: I wish to ask whether any severe anaphylactic reactions to tetanus toxoid have been encountered. My associates and I, in Boston, have used the combined tetanus and diphtheria toxoids as well as tetanus toxoid alone for the last three or four years. Last week a boy with a definite history of allergy received a second dose three months after the original dose of alum-precipitated tetanus toxoid. About an hour after he had left the office his mother telephoned, saying that he could not breathe, that his eyes were about closed and that she thought that he was going to "pass out of the picture." I saw him in about twenty minutes, at which time he had evidence of pulmonary edema and a marked conjunctival reaction. Within a few minutes of receiving a suitable dose of epinephrine hydrochloride he became normal. In three or four hours urticaria with mild systemic allergic reactions developed. After that his course was uneventful.

There arises the question whether there is enough protein in this preparation to warrant testing children who are very allergic, especially before they receive their second dose.

DR. CHARLES HENDEE SMITH, New York: This use of combined toxoids brings up the question of whether it is justifiable to combine prophylactic measures against various infections. The dictum that one should wait three months between immunizations is open to considerable question. In the prophylaxis clinic at Bellevue Hospital this matter is being studied. All sorts of combinations of immunization—against diphtheria, scarlet fever, smallpox, tetanus and whooping cough—have been tried. It seems evident that the injections may be made at very short intervals, or even simultaneously, and that the results are somewhat better, rather than worse, when one or two injections are given together. I think experiences during tornadoes, and so on, have shown that one can give serum for two or three diseases together and get at least as high a degree of immunity, perhaps higher, than when a single serum is given.

DR. ALEXIS F. HARTMANN, St. Louis: The problem of recurrence of tetanus has to be considered, and that brings up the question of whether during the treatment of tetanus with antitoxin one can adopt any measures which stimulate the production of active immunity.

Varney, who, unfortunately, has not published the results of the extensive work which he has been conducting for ten or twelve years in the laboratories of the department of bacteriology, Washington University School of Medicine, has convinced himself that if he inoculates a guinea pig with toxoid and antitoxin at the same time that he infects the animal he can, despite the circulation of huge amounts of antitoxin, still observe the antigenic effect of the toxoid, especially if it is given in repeated small doses intracutaneously at three day intervals.

Because of those observations, my associates and I for five or six years have been using toxoid, given either subcutaneously or intracutaneously, during the active treatment of tetanus. At first we had no observations on the behavior of the antitoxin, but lately Dr. Jean V. Cooke has obtained some interesting figures, about which I should like to ask some questions.

Quite contrary to the usual conceptions, Dr. Cooke noted that when the original dose of antitoxin was as large as 50,000 units or more there occurred a rather slow fall of the level of antitoxin in the blood; of course, the immediate fall was rapid, but it then became slow, so that after sixty, ninety or even one hundred days there was considerably more than 0.01 unit of antitoxin per cubic centimeter still present in the blood. Eventually the antitoxin titer dropped to zero.

From your observations, Dr. Deamer, do you think that such behavior really suggests, as Dr. Cooke is at present interpreting his results, that the injected

antitoxin has persisted for an unexpectedly long period, or do you think that there might be some antigenic effect of the toxoid given at the time the antitoxin was given which caused the antitoxin titers to remain elevated longer than one would have expected but eventually permitted them to drop to a zero level?

DR. JOSEPH STOKES JR., Philadelphia: I think it might be worth while to mention the experience of Dr. Julian Lyon, of Philadelphia, who was interested in obtaining a serum from human beings which might be used as an antitoxin for patients who were sensitive to horse serum. He gave repeated doses of toxoid and later determined the level of antitoxin in the blood. In a number of subjects he was unable to produce large amounts of antitoxin, and also in several instances he observed a marked anaphylactic response, such as Dr. Sisson has mentioned. One subject had a severe anaphylactic shock. From these studies it appeared that there was a marked variation in the individual response in the production of antitoxin.

Another case of some interest is that of a child seen recently who was given toxoid six days previous to the development of a high temperature, ranging from 103 to 104 F., and a stiff neck. The first evidence of difficulty was stiffness just in front of the masseter muscles, and later there was marked pain on both sides of the mandible in the masseter muscles. There was also headache. The spinal fluid showed 470 cells per cubic millimeter, with about 95 per cent lymphocytes, and these increased the next day to 900 cells, most of which were lymphocytes. They disappeared rapidly, and the child recovered in four days. It appeared to be a reaction to the toxoid, although, of course, it is possible that an unknown virus infection was present. The spinal fluid is being studied for some evidence of virus infection, but from the fact that the first signs appeared in the masseter muscles, it seems more likely that the reaction was due to the toxoid.

DR. SAMUEL Z. LEVINE, New York: It might be of interest to note that the prophylactic use of alum-precipitated tetanus toxoid has, I believe, become a routine procedure with the military forces of the United States. That information was received about a week ago; apparently the experience gained in the armies of France and England is being utilized.

DR. JOHN A. BIGLER, Highland Park, Ill.: It happens that my associates and I started a study of immunization against tetanus and diphtheria at about the same time as Dr. Deamer did, and we now have several hundred children in our series. Antitoxin titers in the blood were determined before toxoid was given and one week, two weeks, one month, three months, six months and in some cases, as long as three years afterward. The titers in our series follow curves very similar to those which Dr. Deamer has reported.

There arises the question of course of what amount of antitoxin will afford protection against tetanus. We determined the antitoxin titers in the blood serum of a group of children who received 1,500 units of antitoxin as a prophylactic dose. The children varied in age from 2 to 8 years. The highest antitoxin level found in this group was 0.5 unit per cubic centimeter of serum. The titer remained at that level for about a week; during the second week it was reduced to 0.2 unit, in the third week to from 0.1 to 0.01 unit and in the fourth week to from 0.01 to 0.003 unit.

When these titers are compared with those obtained after immunization against diphtheria and tetanus, one finds that the latter are much higher and remain high for a longer period than the former. Even when the titer decreases to as low as 0.003 unit per cubic centimeter after the second injection, a third injection of the toxoid will cause a rapid increase of antitoxin to a high level.

We have also been concerned about the proper dosage of toxoid. In one series we used two injections of 1 cc. each of the combined material, and we found that it gave just as good results as a series of three injections. With two injections of 0.5 cc. each we found that the average titer was somewhat lower. Three injections of 0.5 cc. each produced about the same titers as two injections

of 1 cc. each. The titers for both groups decreased by the end of three to six months, so that they averaged about the same, that is, about 0.1 unit per cubic centimeter.

We also have figures on the use of unmodified toxoid. With this material the initial height of the antitoxin response is somewhat lower than that obtained with alum-precipitated toxoid, although we consider that the response is adequate.

We have also compared our figures for the results of immunization against diphtheria and tetanus combined with those for immunization against diphtheria alone, and our titers for diphtheria antitoxin were higher when the combined toxoids were used. Also, there seemed to be fewer failures to immunize when the combined toxoids were employed. In other words, with the use of the combined toxoids a greater percentage of the subjects attained immunity than when diphtheria toxoid alone was used.

The same seems to hold true when tetanus toxoid alone is used. The titers seem adequate but are not as high, and they decrease to the same basic level as those which follow the use of the combined toxoids.

There were some failures of immunization in the group of children we have followed up. In the blood of 1 subject after two injections of the combined toxoids no antitoxin for either diphtheria or tetanus was observed in the lowest dilutions which we titrated. Apparently that subject was unable to manufacture tetanus or diphtheria antitoxin. In the blood of another subject who received the combined toxoids there was less than 0.002 unit of diphtheria antitoxin per cubic centimeter, although a good level of tetanus antitoxin developed. In the blood of a third subject after two injections there was less than 0.003 unit of tetanus antitoxin per cubic centimeter, although there was a good level of diphtheria antitoxin. Unfortunately, these 3 children did not return to the clinic, and we were not able to give them a third injection. Other subjects, however, whose titers have decreased as much have responded well after a third, or stimulating, injection.

There is great variability in the individual response to antitoxin production. We have a child who has had a titer of 120 units of tetanus antitoxin per cubic centimeter of blood. Levels of from 10 to 35 units per cubic centimeter of blood are common.

As to the reactions that occur, it is our impression that they are no more severe than, or not as severe, as those following the use of pertussis vaccine. We have not encountered fever except in 2 subjects who had colds, and their temperatures did go up to 105 F. Whether this was due to the material or to the infection I do not know, but we have stopped giving the toxoid when fever is present.

In 2 cases hives developed. One patient I did not see. The other, a physician's child, had several hivelike lesions on the body after the first injection. A few months later a second injection was given and real urticaria developed, which responded to epinephrine hydrochloride.

Many children who were being immunized attended the allergy clinic. Some had eczema, others had asthma and some were receiving hay fever antigens. In none was any increase in the allergic symptoms observed, so I think that one should have no more hesitancy about using the combined diphtheria and tetanus toxoids than about immunizing against diphtheria alone.

We have had about 10 children who have recovered from tetanus whom we have attempted to immunize. The blood serum of these children from one to six years after the tetanus infection did not contain antitoxin in the lowest dilution that we tested, which was 0.003 unit per cubic centimeter. When they were immunized their response after the first injection was no different from that of children who had not had tetanus, and the final response was the same as that of children who had not had the infection.

We have also compared the response to immunization of allergic children with that of children who have not had any symptoms of allergy. There was no better antitoxin response among the allergic subjects than in the group who were not allergic.

DR. MITCHELL I. RUBIN, Philadelphia: Did you find any difference between the titers of the allergic children and those of the nonallergic children?

DR. WILLIAM C. DEAMER, San Francisco: Dr. Sisson's report and the reports of others on the occurrence of an anaphylactic type of reaction are, of course, disturbing. As I indicated, we have not seen any such reactions in a group of 500 infants and a much smaller group of older children. I think it is possible that infants are less likely to have an anaphylactic type of reaction than older children. I should like to know, too, whether the reactions which have been reported occurred after the injection of alum-precipitated toxoid, as the type of toxoid may be a factor.

Dr. Smith and Dr. Bigler stated that the combined toxoids were more effective than either antigen used alone. That is Ramon's contention, and it has been the experience of others with whom I have talked.

I am not sure that I understand Dr. Hartmann's question. If he asked whether an infection due to tetanus produced a stimulus similar to that produced by tetanus toxoid, the answer, apparently, is no. The use of toxoid simultaneously with antitoxin in the treatment of tetanus has been urged by Ramon, and we, too, have used the combination and feel that active immunization can take place after passive immunization quite successfully.

It is interesting to speculate whether the failures of antitoxin production of which Dr. Bigler has spoken would persist after a third injection. I wonder whether he has yet had an opportunity to test whether his subjects will respond to a third, or "recall," injection.

We have worked with the children attending the allergy clinic rather extensively, Dr. Rubin, but the variation in the responses of normal subjects is so pronounced that it is difficult to say whether the allergic subjects have responded better than the others. On the basis of the response of a group of 25 or 30 subjects, it appears that allergic subjects do not respond better than those who are nonallergic, and that is what Gold found for adults.

Pathologic Changes in Chorea. DR. DOUGLAS N. BUCHANAN, Chicago.

There are few reports on the pathologic changes in the brain in chorea. A complete pathologic examination was made of the brain of a 9 year old boy who died of acute chorea and acute rheumatic heart disease. He had choreic palsy of the right side and choreiform movements of the left arm and the left leg. Pathologic changes were observed only in the cortex of the cerebral hemispheres. The lesions were mainly cellular in type and vascular in origin. They were almost entirely confined to the gray matter of the motor and premotor areas, and they were more pronounced on the left side than on the right.

Electroencephalographic records of patients with rheumatic chorea, rheumatic hemichorea and congenital chorea were studied. Rheumatic chorea is associated with a cerebral dysrhythmia which is in some ways like that characteristic of idiopathic convulsions. Hemichorea is sometimes associated with the presence of delta waves in the appropriate regions of the cortex. Congenital chorea is associated with a cerebral dysrhythmia which is more organized than that typical of rheumatic chorea.

The pathologic and electroencephalographic observations are in keeping with the original suggestion of Kinnier Wilson that in chorea the site of the pathologic changes is the motor cortex and not the basal ganglions.

DISCUSSION

DR. BRONSON CROTHERS, Boston: It has been my experience that chorea, more than most of the encephalopathies, is reversible; that is, extraordinarily few of the children whom I have observed are either feebleminded or irregular in their development after the process has subsided; furthermore, very few of them have convulsions.

Dr. Buchanan's evidence seems to suggest that the lesions could hardly be completely reversible from an anatomic standpoint. I wonder whether he has any further evidence on that point.

Dr. Dorothy H. Andersen, New York: Last year my associates and I had the first case of chorea that we have had for a long time in which death occurred during the acute phase of the disease. The child had had one attack of rheumatic fever three years before, about which we knew nothing. We first saw the child the day before death. The patient was sent in from outside the hospital and had been, for most of the illness, under the care of a chiropractor. The child was about 8 years old and showed every evidence of having received very little care.

The rheumatic lesions in the endocardium were unusually large and friable; yet they were quite characteristic. The vegetations were a little less firm than usual. There were minute emboli in the cerebral cortex and also in the basal ganglions. We did not know which localization accounted for the symptoms, which were considered by all the observers as quite characteristic of severe chorea. Certainly, the appearance of the heart was entirely characteristic of acute rheumatic fever.

The question of the pathologic changes in chorea is still unsolved and it seems to me that more data must be collected before one can draw any final conclusions. In going over the literature one finds that in each case the lesions differ greatly from those reported in other cases and there are few cases in which the pathologic changes are reported at all adequately. It seems to me that it would be worth while to report each case completely, since they are so few.

Dr. A. Ashley Weech, New York: I am puzzled by the case of congenital chorea which Dr. Buchanan mentioned and by the intimation that the symptoms could have resulted from cortical irritation. Accumulating evidence suggests that the cortex is not functioning to any appreciable extent at the time of birth. Therefore, I should like to know at what age after birth the movements of chorea actually appear. If the fact that the mother was "on pins and needles" during pregnancy points to the occurrence of fetal choreiform movements, I am puzzled still more that the movements could have had their origin in the cerebral cortex.

Dr. Benjamin Kramer, Brooklyn: Although the electroencephalographic record shows changes in the cortex, this does not exclude the presence of pathologic change in the basal ganglions.

Dr. Douglas N. Buchanan, Chicago: The only thing I can add, Dr. Crothers, is probably of little value. My own feeling is that in the majority of cases of chorea the situation is reversible and that there probably can be a disturbance, essentially of the cortex, which causes the irregular movements of chorea, just as such a disturbance probably causes the irregular movements of a convulsion. In a case of severe chorea some small areas of softening may occur in the cortex which are not sufficiently large or sufficiently numerous to leave permanent signs. You may remember that in the last slide, which was a microscopic section of the changes in the cortex, there were obvious glial proliferation and capillary infiltration; it is at least possible, though this is only an assumption, that that area of softening was produced by the first attack of chorea, which occurred three years before the patient died.

I think Dr. Weech's point about the cortex is well taken. However, it does not necessarily destroy the belief that the potential pathologic change was in the cortex; rather, it does the reverse. It is not stated, and I do not believe it is true, that because the pathologic changes observed were located in the cortex that necessarily the clinical phenomena originated in the cortex. I am not sure that one could absolutely prove the statement that the cortex of the newborn infant does not function at all; I think that it perhaps functions a little and that destroying the cortex destroys the connections between the cortex and the basal ganglions.

The theory that the lower centers of the brain produce the irregular phenomena of congenital chorea is only my idea, and so far as I know there is no proof for it. Nowadays the electrodes for electroencephalographic tracings are normally placed on the surface of the subject's head, without, of course, disturbing him in any way. It is not possible to show accurately any changes in the lower centers of the brain itself. It is possible through more recent work to show changes, or at least to show tracings, which are related probably to the cerebellum. To show changes which might be present in the basal ganglions one would have to do some sort of operation and place the electrodes below the upper layers of the cortex.

Portals of Entry of Poliomyelitis Virus in Primates, with Special Reference to Man. Dr. Howard A. Howe (by invitation) and Dr. David Bodian (by invitation), Baltimore.

Since different animal hosts display widely divergent behavior toward the same virus, it is important to recognize that the observation that the only portal of entry for poliomyelitis virus in the rhesus monkey is the olfactory nerves may not apply to the higher primates, including man. In a series of 6 chimpanzees it was possible to produce typical poliomyelitis by the instillation of potent human stools into the nose, the mouth or the stomach. The disease was produced by the last two methods in the presence of bilaterally sectioned olfactory tracts. On the basis of the distribution of lesions in the brain, the infections produced by the olfactory route were easily distinguished from those caused by the other two methods since only in the first type were the olfactory bulbs and secondary olfactory nuclei involved. In 1 instance in which the intraoral route was used, the disease was very mild and the pathway of the virus could be clearly seen reaching the nucleus of the facial nerve in the medulla along the course of the fifth nerve. The infections produced via the gastrointestinal tract were severe and could not be definitely distinguished from the severe infections produced by the oral route, although the latter did show a somewhat greater predominance of lesions in the nuclei of the cranial nerves.

The olfactory bulbs and the brains of 9 persons who died of the disease have been studied in serial sections. As might be expected, the lesions were extensive, but it was clear that in no instance was there any significant involvement of the olfactory centers. In 1 case in which there were respiratory difficulty and dysphagia there were fresh lesions in one olfactory bulb. Since virus is known to be frequently present in the pharynx and since the secondary olfactory nuclei showed no involvement, it was concluded that these lesions represented a secondary intranasal infection, probably caused by regurgitation through the nose, which had not yet reached the central nervous system. Secondary infections have been shown to occur in experimental animals.

In 1 case in which initial symptoms referable to the bulb were present, there were relatively mild lesions in many susceptible centers but striking and unusual bilateral destruction of the nucleus ambiguus, the source of the somatic motor fibers supplying the muscles of the pharynx and the larynx. There were also changes in the sensory nuclei of the glossopharyngeal and vagus nerves. Of the cases in the human series, this was most nearly comparable to that of the chimpanzee inoculated intraorally. In the remaining cases of the human series the portal of entry could not be definitely distinguished as either oropharyngeal or gastrointestinal, although the latter portal was strongly suggested in 2 of them. It can be concluded that while the nasal tissue has thus been shown to be susceptible, it was not implicated in any of the 9 cases studied.

DISCUSSION

Dr. John A. Toomey, Cleveland: I agree with Dr. Howe that the portal of entry of the poliomyelitis virus cannot be the olfactory area. I wish to com-

pliment him on the completeness of the experimental evidence he has mustered to demonstrate this fact. I should like to supplement what he has said and to present a theoretic method of spread of the virus. I shall assume that the gastrointestinal tract is the portal of entry in this disease and that the virus has an obligate affinity for the gray fibers of the peripheral nerves and is absorbed by them everywhere that virus and nerve meet. I shall also assume that medullation is a normal bar to the spread of the virus. In the human sympathetic nervous system the lumbar and cervical areas are undefended by medullation. With these points and assumptions in mind, a theory of virus spread which I postulated years ago can be described.

The spread of the virus can be likened to the spread of a flooded river. The stream overflows in the area where it has overtopped the banks and along the paths of least resistance. Those paths in poliomyelitis are along the gray fibers of the rami communicantes to the undefended area in the lumbar region, where there is no medullation.

If there is a heavy flood, the virus might also spread along the gray fibers which communicate with other ganglions toward the other undefended area, the gray fibers of the rami communicantes in the cervical portion of the cord.

This theory explains the ordinary type of somatic involvement, but not bulbar involvement. However, I assumed that medullation is a bar to spread; so the situation becomes clear. The peripheral unmedullated fibers of the vagus nerve are in the walls of the viscera. Ordinarily, there is absorption only there, but in some instances there is spread along the vagus itself; in some instances absorption is along the seventh nerve or along other cranial nerves.

The enlargement of the intestinal lymph glands, which is so marked in some cases, is not specific. It does not take much imagination to conceive that in an area where there is possible stasis there might be absorption and enlargement of the local lymph glands.

Dr. Howe has pointed out possible absorption from the tonsillopharyngeal area in 1 animal. Years ago my associates and I obtained similar results when we injected the virus into the seventh nerve or into the circumvallate papillae.

There is experimental evidence to support the belief that the main spread is along the sympathetic and the parasympathetic nervous system. When we dissected the cords of monkeys between the tenth thoracic and the first lumbar segment, leaving only the sympathetic trunk as the connection between the upper and the lower portion of the cord, and injected the virus into the sciatic nerve, the disease was produced in the upper portion of the cord. When we repeated this experiment and injected the virus into the intracerebral area, we recovered the virus from the portion distal to the cut in those areas which were still vascularized.

In the last few weeks Sabin has told me that he has isolated the virus from the sympathetic chain of a human subject. We have isolated it in 2 instances. We have also been able to isolate the virus from the vagus in 1 of 4 instances of bulbar poliomyelitis.

Dr. James D. Trask, New Haven, Conn.: Were there cases in which lesions in the abdominal portion of the sympathetic system were outstanding?

Dr. Howard A. Howe, Baltimore: To answer Dr. Trask's question, we did not examine the abdominal part of the sympathetic system in the case of the patients, because we felt it would not tell us much, inasmuch as in practically all cases of fatal termination virus is present in the stools. In the chimpanzees we found a very high correlation between lesions in the celiac ganglion, for example, and the presence of virus in the stool, regardless of what the portal of entry was; so we felt that it was not critical to demonstrate lesions in the abdominal sympathetic nerves, since such lesions might represent merely a secondary infection.

I think, with Dr. Toomey, that the virus can probably spread along the sympathetic fibers and also along the vagus nerve, but I should not restrict its spread to any particular group of fibers. I think there is just as much evidence for

spread along the somatic sensory and motor fibers, where they are available, as for any other fibers. The data from our study on the chimpanzees definitely implicate the somatic, as well as the visceral, sensory fibers.

DR. JAMES D. TRASK, New Haven, Conn.: What about the lesions up and down the sympathetic chain?

DR. HOWARD A. HOWE, Baltimore: In the chimpanzees there were usually more lesions in the sympathetic chain close to the points where the splanchnic nerves entered. That is as much as I can say.

Fourth Session

Friday Evening, May 23

Beriberi in a Two and a Half Year Old Boy. DR. CHARLES G. KERLEY and DR. EDWARD J. LORENZE JR. (by invitation), New York.

The early history of the patient revealed that because of anorexia and habit vomiting the food intake for several months consisted almost entirely of milled white cereal, which was given frequently and in large portions. During the preceding four weeks there had been a loss of 4 pounds (1.8 Kg.) in weight. Signs of an unusual illness had been observed for two weeks. The disorder was unusual in that the symptoms were objective and in no way constitutional. The boy preferred to sit, quiet and undisturbed; manipulation was accompanied by crying and was strongly resisted. Bathing and the use of the toilet in the customary position soon became impossible. In walking the posture had changed, the trunk being held rigidly, and all voluntary movements ceased.

There was no elevation of temperature; nutrition and muscular development were fairly satisfactory. All of the organs, including the heart and lungs, were normal, and examination of the blood and urine gave normal results. The patient evidenced great pain during the necessary manipulations of the examination and cried bitterly. There were entire absence of flexibility of the spinal column; the pain and tenderness seemed to be located chiefly in the thoracic, abdominal and lumbar muscles.

When he stood erect, the trunk was held rigid in a modified opisthotonos position. In ascending stairs he rested the right hand on the balustrade and pulled and put the left hand on the left knee and pushed in order to ascend. It was impossible for him to arise from the supine position; in order to get up from his hands and knees he had to hold on to the furniture. The symptom complex was that of pseudohypertrophic muscular dystrophy with acute peripheal polyneuritis. Mentally, he was somewhat precocious and highly combative.

A diagnosis of avitaminosis of the beriberi type was made, and it was suggested that he eat three meals daily of milk, meat, eggs, vegetables and fruits, with water between meals. In addition, we prescribed 15 minims (0.93 cc.) of percomorph liver oil 50 per cent, and 50 mg. of nicotinic acid in divided doses daily; the dose of nicotinic acid was reduced after three days to 12.5 mg. because of a cutaneous eruption.

The child was seen eleven days later, when a dramatic improvement was apparent. There was no resistance to manipulation or objection to the bath or use of the toilet; he ascended stairs in a normal fashion and climbed on and off a bench unaided.

The question naturally arises of what bearing avitaminosis B might have in pseudohypertrophic muscular dystrophy. Is pseudohypertrophic muscular dystrophy a result of persistent avitaminosis B?

It was interesting that the child's condition had been satisfactory except for the neuritic manifestations and that the results of the physical examination were largely normal. This feature is commented on by Mouriquand (*Arch de méd. d. enf.* **42**:673-690, 1939).

"Subjects may appear to be in good or relatively good health for a long time on a diet deficient in accessory factors and ill balanced in composition, and during this time no clinical signs call attention to any ever so mild disorder related to the nutritional deficiency which may be present. They are looked on as healthy until a precipitant factor (which may be alimentary, physiologic or infectious in origin) exteriorizes, as it were, the hidden ill balance and turns this asymptomatic state into a symptomatic one."

DISCUSSION

DR. LAWRENCE T. ROYSTER, Charlottesville, Va.: It is only occasionally that my associates and I at the University of Virginia Hospital see patients with a condition which can be diagnosed as subacute, subclinical beriberi. However, farther south, in Georgia, Alabama, the southern part of South Carolina and Louisiana, one sees a number of patients with undoubted clinical beriberi. My colleagues in that part of the country have told me of cases of a disorder which unquestionably is of the same type as that Dr. Kerley has described except that edema is present.

The patients I have seen had neurologic changes; Dr. Kerley asked me specifically whether they had hyperesthesia or anesthesia. Some had one and some the other. There is an almost total lack of ability to utilize the lower extremities in cases of the advanced type. Almost inevitably edema is present, a feature which is interesting in that it predominates in the upper part of the chest. In their textbook Holt and McIntosh have given a good picture of this disorder. Edema is also present in the lower part of the abdomen and in the extremities.

There may be anesthesia or hyperesthesia, but the outstanding characteristic is tachycardia. In almost every instance, according to a number of colleagues in the South with whom I have talked, tachycardia is an almost invariable manifestation of this condition.

I was asked the other day what avitaminosis B_1 is and how it is manifested. In my opinion, avitaminosis B_1 is merely subclinical beriberi. It cannot be classified as beriberi, but it responds to the same treatment. The few patients with this condition whom I have seen responded dramatically to administrations of thiamine hydrochloride. The tachycardia was rapidly relieved, and within ten days or two weeks the whole condition cleared up. I think that this disorder is far more common than has been realized and that the farther south one goes the more frequently it is seen.

DR. CHARLES G. KERLEY, New York: The boy certainly had tachycardia. The heart was pounding, and the pulse could be counted with difficulty; this we attributed to the fear of being manipulated.

The most outstanding feature of the case was the prompt recovery from an unusual symptom complex through the utilization of a component of the vitamin B complex other than thiamine hydrochloride.

Fecal Fat Excretion by Premature Infants. DR. HARRY H. GORDON (by invitation) and MISS HELEN MCNAMARA (by invitation), New York.

Fecal fat was determined in a total of 98 observations lasting three to seven days on 43 thriving, prematurely born and 11 full term infants less than 2½ months old. In 65 observations the fecal fat partition was also determined. The premature infants were fed human milk, cow's milk or a cow's milk mixture in which the cream had been replaced by olive oil. For each of the two latter types of diet two levels of fat intake were employed, the one supplying 4 to 5 Gm. and the other 2 Gm. of fat per kilogram per day. For the full-term infants the diets consisted either of cow's milk or of the olive oil mixture. Adequate amounts of a

concentrate of vitamin D or of vitamins A and D were given daily to each infant. The calcium contents of all of the diets except the human milk were approximately the same.

The excretion of fecal fat ranged from 1 to 4.1, from 0.6 to 3.3 and from 0.5 to 3.0 Gm. per kilogram per day for the premature infants fed cow's milk (20 observations), the olive oil mixture (35 observations) and human milk (12 observations) respectively, and exceeded 1.5 Gm. in approximately half of the observations on each type of milk. For the full term infants, the excretion of fecal fat exceeded 1.5 Gm. in only 1 of 12 observations. In the 19 observations on the half-skimmed milk mixtures, the excretion of fecal fat ranged from 0.5 to 1.3 Gm. per kilogram per day. The level of 60 per cent of the dry weight of the feces as fat served to divide those infants who excreted more from those who excreted less than 1.5 Gm. of fat per kilogram per day.

The studies of fecal fat partition indicated (1) that premature infants did not split olive oil but did split butter fat as well as full term infants; (2) that both groups of infants split butter fat better than olive oil, and (3) that the percentage of fecal fat present as soaps plus free fatty acids was determined by the type of dietary fat and was not related to the total amount of fat excreted. The fecal fat partition of a single full term infant with congenital stenosis of the common bile duct was similar to that of premature infants. The feeding of dried ox bile in small amounts to 2 premature infants increased the percentage of fecal fat present as soaps plus free fatty acids but did not decrease the total amount of fat excreted.

Dr. L. Emmett Holt Jr., Baltimore: It is difficult to discuss intelligently such a thorough piece of work as that of Dr. Gordon without an opportunity to study his data in some detail. He presented a wealth of interesting observations. His results and his conclusions differ in some respects from those which Dr. Tidwell and I reported a few years ago, and I should like to comment briefly on these differences.

Dr. Gordon's results fail to show any striking superiority of absorption of olive oil, as contrasted with butter fat, as our experiments had shown. It is only fair to point out, however, that the conditions in the two sets of experiments were different. In the experiments which Dr. Tidwell and I carried out the fat was the only variable, whereas in Dr. Gordon's experiments there were other variables, which may or may not have affected fat absorption. If I understood Dr. Gordon correctly, his olive oil feedings consisted of the commercial product Olac, a preparation which, in adidtion to the substitution of olive oil for butter, contains casein and a malt dextrin preparation. His butter fat feedings, on the other hand, consisted of cow's milk supplemented with carbohydrate so as to yield a percentage distribution of calories approximately identical with that of the "olive oil" feedings. I do not for a moment doubt Dr. Gordon's ingenuity in accomplishing this identity of percentage compositions, but I am somewhat at a loss to know how it was brought about. For example, in Olac the butter fat is quantitatively replaced by olive oil; the subsequent addition of casein is, therefore, bound to alter the protein-fat ratio of the feeding, a ratio which cannot be restored by dilution or addition of carbohydrate. A second point is that even if the total protein intake were equalized in Dr. Gordon's experiments important qualitative differences would still remain, for a considerably larger percentage of the protein of the Olac is casein, which might be expected to have a more unfavorable influence on fat absorption than lactalbumin. I am not prepared to say that the differences between Dr. Gordon's results and ours are due to such differences as I have mentioned, but it seems to me that they might explain the discrepancy in the results.

Dr. Gordon was conservative in stating his conclusions, but there were implications in what he brought out with which I should like to disagree. One deduction one should be cautious about drawing is that a more rapid gain in weight, such as may be observed when carbohydrate is substituted for a part of the fat in the diet, indicates superior nutrition. The phenomenon of a temporary gain in weight on a carbohydrate diet and the converse, a temporary loss or arrest of

weight on the reintroduction of fat, is familiar, but its significance is still far from clear. Carbohydrate metabolism apparently requires more water than fat metabolism, and more water is retained in the body under these conditions, until a new balance is established. An increase in carbohydrate intake is also followed by a temporary increase in retention of nitrogen with a striking qualitative shift in the nitrogen partition of the urine, urea excretion being decreased and uric acid excretion increased. Until the significance of such changes is understood, it seems to me unwise to conclude that premature or normal infants, because of temporarily better weight gains, should be fed formulas low in fat. Further metabolic studies, and many of them, of the type which Dr. Gordon and his collaborators have carried out will be needed before it will be possible to say decidedly what is the ideal feeding for the full term and the premature infant.

DR. HARRY H. GORDON, New York: In Dr. Holt's observations the infants were fed a skimmed milk powder into which different fats, such as olive oil or butter fat, were incorporated. As he pointed out, the infants in the present study were fed a dilution of ordinary powdered whole milk reenforced with sugar, and in the observations on olive oil we used a commercial preparation in which olive oil had already been homogenized into the feeding. For the 4 infants studied in repeated observations on feeding two types of fat, the diets were constructed to give the same amount of fat and the same total caloric intake per kilogram of body weight. Under these conditions the calcium and total mineral intake were virtually identical, and the slight differences in protein and carbohydrate content could hardly be considered significant. In the whole group of infants there was so much variation from one infant to the other that average figures could not be used in support or in refutation of any claims concerning the advantages of one fat over another, especially since there was so much overlapping in the range of results on fat excretion. No observations were made with soy bean oil as a source of dietary fat.

As to the desirability of feeding premature infants half-skimmed milk mixtures reenforced with sugar when breast milk is not available, in view of the experience Dr. Powers has had in New Haven with much larger groups of infants than we have studied, we have no hesitancy in recommending the use of such mixtures over a long period. In the last edition of the textbook by Holt and McIntosh it is stated specifically that it is the safest procedure in the long run to feed premature infants the smallest amount of food which will result in a satisfactory gain in weight. We believe that such weight gains are attained most readily by using half-skimmed milk mixtures provided additional amounts of vitamins A and D, as concentrates, are supplied.

As Dr. Holt has implied, many premature infants gain satisfactorily on diets which are not low in fat. This is to be expected from the fact that not all premature infants have a defect in fat absorption. Only some of them have it. In many of them the defect is not of clinical significance; that is, the total amount of fat excreted may be between 10 and 15 calories per kilogram. We did find, however, that in approximately one third of our observations on premature infants fed whole milk mixtures over 20 calories per kilogram were lost as fecal fat. We feel that by all standards this is excessive.

A study is now in progress in which premature infants admitted to the nurseries of the New York Hospital are routinely separated according to birth, weight, sex, race and plurality of birth and are then fed in rotation breast milk, a simple evaporated milk formula and the half-skimmed milk mixture of Dr. Powers. It is hoped that at the end of ten years, with constant nursing conditions and with constant environmental conditions, we may be able to draw some conclusions about the relative merits of these feeding mixtures, at least under the conditions of nursery practice in a large hospital. In addition, a statistical analysis is being made by the United States Children's Bureau of the feeding records of all premature infants admitted to the New Haven Hospital and the New York Hospital during the past eight years.

Pathogenesis of Celiac Disease. Dr. Charles D. May (by invitation), Dr. Kenneth D. Blackfan and Dr. John F. McCreary (by invitation), Boston.

This communication presents a summary of the results of studies undertaken to determine the cause of the defective absorption of fat in celiac disease.

It is essential that the diagnosis of celiac disease should be used only in the cases of infants and children who have all of the features of the celiac syndrome (characteristic feces, wasting, distention of the abdomen, low curves for dextrose and vitamin A absorption and "clumping" in the roentgenograms of the gastrointestinal tract) in the absence of any other condition which could produce these features. There must be improvement from proper therapy before the diagnosis can be considered established. The cases in this study satisfied all of these criteria.

The primary fault in celiac disease is an unexplained defect in the intestinal absorption of fat. The most important known factors involved in the absorption of fat by normal persons are: (1) mechanical mixing of the food in the gastrointestinal tract, (2) emulsifications, (3) lipase, (4) bile salts, (5) phosphorylation in the intestinal mucosa and (6) a normal lymphatic system.

We have investigated each of these factors in our cases of celiac disease, and it appears that it is some defect in the intestinal mucosa which accounts for the defective absorption of fat in that disease.

On the basis of several considerations it seemed reasonable to view celiac disease and the defective absorption of fat as due to a deficiency of some extrinsic or intrinsic factor. We were led to seek such factors in the cruder liver extracts and the vitamin B complex.

After parenteral injection of large doses of liver extracts and the vitamin B complex in 10 cases of definite celiac disease we observed the following results:

1. The absorption of fat was promptly improved, in contrast to the slow improvement achieved by dietary therapy.

2. A corresponding rapid improvement in the clinical features occurred.

3. At the same time the absorption of dextrose, the roentgenograms and the motility of the gastrointestinal tract returned to normal.

Our objective data suggest that the course of celiac disease is favorably influenced by a substance or substances in the vitamin B complex and/or liver extracts. This may be through improvement in the intermediary metabolism, particularly of fat, in the intestinal mucosa. We are at present seeking to locate the active principle or principles in the substances we have injected parenterally and to investigate the mode of action in cases of celiac disease.

DISCUSSION

Dr. Samuel Z. Levine, New York: I should like to ask whether the results of the vitamin A absorption tests were checked in any of the observations by chylomicron counts after the administration of crude liver extract. It has been my experience that the use of crude liver extract does not invariably cause more rapid improvement in celiac disease, and I wonder whether such exceptions have an explanation.

Dr. Warren R. Sisson, Boston: I had the opportunity to observe 2 patients recently whom Dr. May and his associates have followed up rather carefully, and I do not think they are in the group for which he presented data here.

I should like to ask Dr. May how long it is necessary to continue the parenteral injections of vitamin B complex and liver extract. One of my patients with typical idiopathic celiac disease responded miraculously to the parenteral use of these two substances, and the injections were continued for about three weeks. The child was sent home with instructions to take solution of liver and vitamin B complex (by mouth) and continued to do very well. An infection of the upper respiratory tract developed, and the child lost 2 pounds (0.9 Kg.) in the course of the next two weeks, but soon returned to normal.

DR. DOROTHY H. ANDERSEN, New York: I should like to ask, Dr. May, if you have any evidence that there had been a previous dietary deficiency in your cases of celiac disease. Would you suggest a dietary deficiency as the fundamental cause of celiac disease or failure of fat absorption?

With respect to administration of liver extract, my associates and I have not had the experience that Dr. May has had with the vitamin A absorption curves, but we have had some dramatic clinical experience with the combined use of vitamin B complex and liver extract, which we began several years ago more or less empirically and which we have continued because it worked.

DR. BENJAMIN KRAMER, Brooklyn: Several years ago Dr. Benjamin gave a report at a meeting of the Society for Pediatric Research on a child he thought had pernicious anemia. The blood picture was that of pernicious anemia, and the question was whether the disorder was true pernicious anemia or celiac disease with a pernicious anemia blood picture. He treated the patient with parenteral injections of liver extract in addition to prescribing a normal diet and achieved really astounding results. Not only did the blood respond promptly to the therapy, but there was marked improvement in the clinical condition. He subsequently proved that the intrinsic factor was lacking in the gastric juice.

His treatment did not include administration of the vitamin B complex, except such amounts as must have been present in the normal diet. Since then the patient has done well with oral administration of liver extract, although previously this had no effect.

I wonder whether administration of the liver extract without the addition of the vitamin B complex, other than that present in any well balanced diet, would have an equally good effect.

DR. HARRY H. GORDON, New York: Administration of a whole liver extract alone to 2 premature infants whom I observed was entirely without effect on the excretion of fat.

DR. SAMUEL AMBERG, Rochester, Minn.: My associates and I had an interesting case, that of a child with celiac disease who did well under the usual treatment without liver extract, though recovery took some time. A slight infection developed and he lost considerable ground. At the time of the loss of weight, there was marked macrocytosis, but no other signs of blood dyscrasia or disease, and the administration of liver extract was highly effective.

DR. CHARLES D. MAY, Boston: I should like to answer the questions together, since they are closely related.

I neglected to say that we have similar data for 18 patients with celiac disease who were treated by dietary therapy alone. Nine of these have shown no improvement in the absorption of vitamin A even after an average of two years of dietary treatment, with a range of from four and a half months to six and a half years. Nine of them have shown improvement in the absorption of vitamin A, with the use of the special diet alone, but the average time required was two years. The shortest time in which any patient showed improvement through dietary treatment alone was three and a half months, in contrast to the consistent improvement within three weeks of therapy with liver extract and vitamin B complex.

We have not made any chylomicron counts.

It is not surprising that the use of liver extract alone may at times have yielded disappointing results, because we, too, have had such experiences. We have used crude liver extracts prepared by Dr. Castle, who assured us that the extract contained everything wholesome in liver, and yet this extract by itself produced no improvement in our patients with celiac disease, as measured by clinical indexes or by the absorption of vitamin A. We have treated other patients for many weeks with parenteral administrations of liver extract alone, without improvement. It was that consideration which led us to include the use of the vitamin B complex as well. We were seeking blindly for some

factor which would influence the defective fat absorption. It seemed logical that a disease which had such an insidious onset and which gradually yielded to careful dietary therapy, with a return to normal health, would fulfil some of the criteria of a deficiency disease.

We are not yet able to say how long treatment must be continued. It is certain, however, that, as in other deficiency conditions, particularly sprue and pernicious anemia, any intercurrent infection will complicate the therapy, to make it ineffective or require the administration of larger doses.

Two patients with celiac disease were treated without receiving benefit from the injections. In spite of careful dietary treatment for two years or more, they still showed very low rises in their curves in the vitamin A absorption test. Conceivably, therefore, when the condition has been of long standing the dose required may be much greater and the patient may also have to be treated longer to secure beneficial results. The only other regularly occurring signs similar to those of the vitamin B deficiency group which we have seen in patients with celiac disease have been pellagra-like cutaneous lesions on the hands and, rarely, macrocytic anemia with smooth tongue.

It is entirely conceivable that in the population are a few subjects whose requirements for the vitamin B complex are greater than those of the majority and that such measures as introducing solid foods into the diet at an early age may increase the requirement for some of the constituents of the vitamin B complex, as is known to occur with regard to vitamin B_1. Celiac disease occurs in only 1 of about every 1,500 patients, in our experience. It would not be surprising to discover that the patients with celiac disease were those whose requirements of the vitamin B complex, for one reason or another, were greater than normal, particularly if they had had a series of infections previous to the development of the syndrome.

Pancreatic Enzymes in the Duodenal Secretions of Normal Children and of Those with the Syndrome of Pancreatic Insufficiency.

Dr. Dorothy H. Andersen (by invitation), New York.

The clinical diagnosis of cystic fibrosis of the pancreas presents difficulties, especially before the development of the infection of the respiratory tract which is almost uniformly the cause of death. The assay of pancreatic enzymes in the duodenal secretion of patients suspected of having the disorder seems to offer the best means of diagnosis. The pancreatic enzymes in the duodenal secretion have therefore been measured in cases of suspected pancreatic deficiency, in cases of chronic diarrhea in early infancy, in cases of celiac disease in later infancy and for a group of control cases of children of comparable ages without symptoms referable to the gastrointestinal tract. The diagnosis of pancreatic deficiency has been made by this means in 15 cases; in all of them the clinical course was characteristic of the disease, and in 5 the diagnosis was confirmed at autopsy. For the controls the amylase values were minimal during the first two months, with a rapid increase during the first year and fairly constant values after that. The infants with prolonged diarrhea or the celiac syndrome had amylase values which were significantly low for their ages. Three patients with extreme marasmus from prolonged diarrhea had low values for all three enzymes, but after clinical recovery the figures returned to normal. The figures for trypsin and lipase were within the normal range in all cases except those of pancreatic deficiency and those of marasmus. The assay of trypsin is the most reliable means of obtaining a definite diagnosis of pancreatic deficiency. Assay of serum amylase is of no value in the diagnosis of pancreatic deficiency, since the figures are variable and usually lie within the normal range.

DISCUSSION

Dr. Arthur H. Parmelee, Oak Park, Ill.: Dr. Andersen's paper is of great importance, particularly from the standpoint of prognosis. As a means of

differentiating pancreatic steatorrhea from celiac disease by other than clinical methods this method may prove to be of importance, because celiac disease when properly treated offers a fairly favorable prognosis, whereas congenital pancreatic steatorrhea has an almost 100 per cent fatal outcome, as I reported at a meeting of this society some years ago, and has a familial tendency.

Dr. Charles G. Kerley, New York: Clinically, it has seemed to me that cow's milk fat is particularly difficult for the child with celiac disease to assimilate. I wonder if Dr. Andersen has observed that cow's milk fat is more difficult for such children to utilize than other forms of fat.

Dr. George M. Guest, Cincinnati: The results of some studies of blood amylase made in 1926 at the Children's Hospital in Boston might be cited here in corroboration of some of Dr. Andersen's observations. The activity of amylase (then called diastase) was measured by determination of the amount of dextrose split from starch by the blood. Amylase activity was found to be very low in the blood of infants with gastroenteritis and of infants who were "doing poorly," that is, failing to gain in weight although not acutely ill; on the other hand, it was high in the blood of infants with pneumonia.

Recently, in Cincinnati, my associates and I embarked on similar studies, using an improved chemical method for the determination of the amylase activity of blood serum. These studies yielded data which closely parallel Dr. Andersen's observations on normal infants: The serum amylase activity was found to be very low at birth and to increase slowly during the first few months of life.

With regard to the significance of these changes in blood amylase activity, I should like to ask Dr. Andersen what she believes to be the source of blood amylase—whether it is absorbed from the pancreas or the intestinal tract or whether, as some physiologists have maintained, it is formed in the liver. The observations reported here may have widely different significances according to different concepts concerning the origin of the blood amylase. For instance, diarrhea might lead to great wastage of amylase that is secreted into the intestinal tract and lost with the stools, such a loss of enzyme being comparable to losses of electrolytes which occur with diarrhea. On the other hand, if amylase is absorbed directly into the blood from the pancreas or from some other organ, the depression of amylase activity in the blood observed in certain conditions must be explained otherwise.

Dr. Henry J. Gerstenberger, Cleveland: In the discussion of Dr. Warkany's paper of last evening, I made the statement that one could diagnose the presence of pancreatic disease in young infants rather easily if one gave them carotene in oil and watched the diapers. I neglected to ask for all of the slides which I had on the table. I took the first and forgot about the rest. (Slide) This colored slide of a diaper stained with carotene in oil is from the case of biliary atresia to which I referred last evening and not from a case of pancreatic fibrosis; the diapers appear the same in both diseases except that in the cases of pancreatic disease which I have observed the loss of carotene in oil is greater. It is my opinion, and this statement is not in contradiction to what Dr. Andersen has said, that if an infant who is 8 to 12 weeks old and is somewhat emaciated and has symptoms of involvement of the respiratory tract with little or no fever is given even small amounts of carotene in oil (25 to 50 drops before each feeding) one can determine the presence or absence of pancreatic fibrosis by observing the diapers; congenital atresia of the biliary tract, of course, can be excluded by simply looking at the patient, who will be yellow if he has this disease.

(Slide) This colored slide, which is from the case of biliary atresia to which I referred last evening, clearly shows that the lower halves of both upper and lower incisor teeth are decidedly yellow (bile stained), while the upper halves are white. This change must have occurred soon after the opening up of the atretic bile duct. The photograph of the child's face was taken recently, when she was 15 months old and weighed 8,578 Gm. She is now normal, though she was a premature infant who weighed 1,600 Gm. at birth and somewhat later her weight

fell to 1,400 Gm. At that time the icteric index was 250. Whether the very large doses of vitamin A contributed to the recovery of this infant I do not actually know, of course, but it is certainly possible.

DR. DOROTHY H. ANDERSEN, New York: Dr. Parmelee's experience with the tragic families which have lost one baby after another because of pancreatic deficiency parallels my own. My associates and I have seen a number of such families. On the other hand, in the past year in the families of 3 of our patients with pancreatic fibrosis normal siblings have been born; so we are not entirely pessimistic in our counsel to parents.

I had hoped that if the diagnosis could be made before the babies became too ill therapy could be attempted with some hope of success. Treatment of pancreatectomized animals has succeeded well enough, and older patients whose pancreases have been removed because of carcinoma seem to get along fairly well. If such children can be brought safely past the period of rapid growth their treatment should be less difficult. Whether this is possible I do not yet know. We have 2 patients well on the way to success, and we have had a number of failures.

Dr. Kerley's question in regard to cow's milk fat is pertinent to this problem, too. One of the patients who is doing well and who has had all the signs of pancreatic fibrosis except the terminal marasmus was in the hospital for a study of what he could eat and how much and what type of fat he could utilize. Our analyses are as yet incomplete, but it has seemed that the quantity of fecal fat was less when we used corn oil instead of butter fat. One obvious difference between the composition of butter fat and that of corn oil is in the number of atoms with double bonds. Of course, the study should be repeated and enlarged to include a series of infants. My experience with patients with classic celiac disease is too limited for me to draw any general conclusions.

When I first started making determinations of serum amylase I was much surprised to find very low values for all infants under 6 weeks and for most infants under 3 months of age. The value for amylase was also low or zero for many others who were losing weight and were not doing well for a variety of reasons. When my technics for measuring enzymes in duodenal secretion were established, I obtained and correlated data on the amylase content of both the blood and the duodenal secretion for about 50 patients. I was interested to discover that whenever the value for amylase in the duodenal secretion was below 10 units per cubic centimeter, and often when it was below 20 units, no amylase could be detected in the serum. Above that level there seemed to be no correlation between the amount of amylase in the serum and that in the duodenal secretion. The critical level for the amylase in the duodenal secretion was somewhere between 10 and 15 units per cubic centimeter. Above that there were various amounts of amylase in the serum; below it there was none. Correlation of the level of serum amylase with age gives a regular curve, with a probable error of the mean which makes a pattern very similar to the pattern for amylase in the duodenal secretion except that the increase with age is less marked and the adult levels are reached at about the age of 2 years.

It seems to me that serum amylase probably arises in the pancreas. I do not know that it could not arise in the salivary glands, and I have no new data on that question. I have studied the breakdown of sugar in the liver in connection with another disease, and I am sure in my own mind that the amylase in the blood and the amylase in the pancreatic juice have little to do with the liver.

Dr. Gerstenberger's results with administering carotene in oil, I am sure, could be confirmed in many cases of pancreatic deficiency. The test is not absolutely diagnostic, because one probably could obtain the same results for one of the babies with marasmus mentioned in connection with the last slide, whose digestion was at the same level of impairment as that of some of the babies with pancreatic disease. It is true, however, that the majority of the children with pancreatic fibrosis excreted a very high percentage of the dietary fat, sometimes

split and sometimes unsplit; the observations varied a good deal from patient to patient but were fairly constant for the same patient when the experiment was repeated with the use of the same diet.

Glycogen Disease. Dr. Edward M. Bridge, Dr. L. Emmett Holt Jr. and Dr. Charlotte Kajdi (by invitation), Baltimore.

Two patients with glycogen disease, aged 16 months and 5½ years, had the usual picture of enlarged liver, fasting hypoglycemia and ketosis and decreased epinephrine hyperglycemia. The older child was also dwarfed. Material obtained by biopsy, the blood and the urine were studied, and observations on general metabolism were made in a metabolism chamber.

Biopsy showed that the liver was loaded with glycogen (concentrations of 15.4 and 13.9 per cent, respectively), which was stable when allowed to stand at room temperature but was broken down when mashed with normal liver or incubated with a buffered solution of pancreatic amylase. The concentration of glycogen in the muscles was extremely high (4.7 per cent) in the older child but was normal in the younger. Sections showed that the liver cells were greatly distended with glycogen and contained only small amounts of cytoplasm.

The glycogen in the blood was increased and was present almost entirely in the blood cells. Reprecipitation of this "glycogen" gave a substance which reacted in every way as normal liver glycogen does.

Metabolic studies on the younger patient showed a normal respiratory quotient between feedings. However, if one of the regular feedings given every four hours was omitted the respiratory quotient decreased rapidly and within two hours was below 0.80. The blood sugar fell to hypoglycemic levels in a manner corresponding to the rapid fall of the respiratory quotient. Thus, in spite of the known excessive quantities of glycogen in the liver, the child reacted to starvation in a way suggestive of almost complete absence of carbohydrate reserves.

The nitrogen balance of the older child was negative. It is suggested that such loss of nitrogen results from the increased gluconeogenesis which develops to compensate for the hypoglycemia and the useless glycogen stores. Such a negative nitrogen balance offers a possible explanation for the retarded skeletal development.

In conclusion, it is felt that the various manifestations of glycogen disease can be understood as secondary or tertiary reactions to the central inability of the organism to mobilize its glycogen stores.

Experiences with the Parenteral Administration of Vitamin D. Dr. Henry J. Gerstenberger, Cleveland.

Even though rickets, which in human infants is a sunlight deficiency disease, can readily be prevented during the months deficient in sunlight in a variety of ways, it is not being prevented in the degree to which it should, especially in breast-fed infants, for many reasons which in the last analysis center about such qualities of the individual mother as attitudes, health and intelligence.

For these reasons, and for others, the method of giving by mouth one dose of the antirachitic factor large enough to carry the infant through the winter without the development of rickets has been advocated and adopted abroad. The dose required to obtain this result, however, is very large, namely, 600,000 U. S. P. units of vitamin D. On the basis of studies made at the Babies and Childrens Hospital of Cleveland on rachitic (sunlight-deficient) monkeys, it was learned (1) that vitamin D_3 (activated 7-dehydrocholesterol) is definitely superior to vitamin D_2 (calciferol), (2) that vitamin D_3 dissolved in oil is superior to that dissolved in propylene glycol, (3) that the subcutaneous administration of vitamin D_3 in oil can be carried out without the appearance of harmful effects (local or general), (4) that the duration of the healing effect is substantially pro-

longed over that obtained with peroral administration and (5) that the dose required is very much below the peroral dose.

Subsequent observations made at the hospital on infants admitted because of rickets likewise showed the harmlessness of the parenteral administration of vitamin D_3 in oil and its decided superiority over the peroral administration. One 8 day old infant weighing 3,400 Gm. was protected for over five months by giving him parenterally a dose of 25,000 U. S. P. units of vitamin D, and another infant on the twenty-third day of life, when he weighed 3,500 Gm., was given 12,500 U. S. P. units. A premature infant, 3 weeks old, who weighed 1,635 Gm., was similarly protected by a dose of 25,000 U. S. P. units given parenterally.

On the basis of these results, a practical attempt was made during the winter of 1940-1941 to prevent rickets in young infants at home. With the cooperation of the division of health of the city of Cleveland, the plan was kept in operation in two districts between Oct. 31, 1940 and April 10, 1941. The dose of 25,000 U. S. P. units was administered to 134 infants between October 31 and January 2 and the dose of 12,500 U. S. P. units to 26 infants between December 5 and January 2.

Roentgenograms were taken before or immediately after the injection and as often as possible thereafter at intervals of from four to eight weeks. Determinations of calcium and phosphorus were made, for psychologic reasons, not at the beginning but toward the end of the observation periods.

Of the total of 237 subjects with whom contact was made, data on 160 could be used, inasmuch as they had complied with the following conditions: (1) The infants received the full dose decided on; (2) they had been observed for twelve weeks or longer (66 per cent actually had been observed for sixteen weeks or longer); (3) they had had two or more roentgenograms (100 per cent had had 2, 88 per cent had had 3 and 55 per cent had had 4 or more roentgenograms), and (4) they had not received additional antirachitic therapy of any significance. Of the 237 subjects, 13 were used as active controls; that is, they came to the dispensary with active rickets at some time during the period of study and so demonstrated that the sunshine available in Cleveland during the test period was not adequate to prevent against rickets or decidedly to influence rickets once it was established. The age of 84 per cent of the 160 infants was less than 3 months and that of 75 per cent less than 2 months. Ninety per cent had satisfactory curves for weight gain, from the standpoint of the development of rickets, and 70 per cent had curves that were normal or above normal.

The results of the calcium and phosphorus determinations for 55 of the 160 patients were normal. Ninety-six per cent of the determinations were made after an interval of twelve weeks or longer, 70 per cent after fourteen weeks or longer and 44 per cent after sixteen weeks or longer. The roentgenograms of 159 of the 160 infants were normal at the end of the observation period. In the roentgenogram of 1 infant the distal ends of the ulna and the radius were queer but not typically rachitic.

The final conclusion is that vitamin D_3 dissolved in oil given parenterally in a single dose of either 25,000 U. S. P. units of vitamin D beginning Oct. 31, 1940 or in a dose of 12,500 U. S. P. units beginning Dec. 5, 1940 was adequate to protect against rickets 159 of 160 infants coming principally from the poorest families of Cleveland. The 25,000 U. S. P. unit dose is one twenty-fourth and the 12,500 unit dose is only one forty-eighth of the accepted necessary peroral dose of 600,000 U. S. P. units.

It is suggested that the parenteral route of administration of vitamin D_3 is more physiologic than the peroral; the fact that both human milk and cow's milk are practically devoid of antirachitic power speaks in favor of this theory.

DISCUSSION

DR. FREDERICK F. TISDALL, Toronto, Canada: I should like to know what Dr. Gerstenberger's results would have been if he had given every second baby

an injection of plain oil as a control. I ask this because several years ago my associates and I spent about three years studying the effect of various doses of vitamin D. We gave every second subject capsules of what we called "viosterol A," which, in reality, contained no viosterol, but the mothers did not know that. As the result of that procedure, we were able to observe some 300 or more infants in Toronto who received absolutely no antirachitic therapy.

Dr. Gerstenberger has mentioned that Cleveland is a little smokier than other cities; he would have to have a different base line than we had in Toronto, but we found that 50 per cent of the infants who received no antirachitic therapy at all had perfectly normal bones throughout the winter, as determined on follow-up roentgenograms taken at periodic intervals.

In 13 per cent of the babies marked rickets developed. In a total of 35 per cent some degree of rickets developed, and there was an additional 15 per cent who Dr. Martha Eliot considered showed extremely slight evidence of rickets. So we were able to say that in 50 per cent of the babies rickets would not develop. Therefore, to be strictly correct, I think Dr. Gerstenberger would have to modify his statement that the bones of the babies were perfectly normal as the result of giving the vitamin D, because if the same conditions held in Cleveland as in Toronto, 50 per cent of the babies would have had normal bones in any case. But that does not detract from the value of Dr. Gerstenberger's paper.

DR. BENJAMIN KRAMER, Brooklyn: There are in the literature at least three contributions in which the relative values of so-called metabolized milk and irradiated milk are compared and the minimal preventive and curative doses are established. Since the antirachitic effect of irradiated milk is due to vitamin D_3 and that of metabolized milk is due to vitamin D_2, such comparative studies should serve as a measure of the relative potency of these two forms of vitamin D. All of these contributions—and one of these is by Dr. Gerstenberger himself—indicate clearly that there is no definite difference in the clinical potency of these milks. Therefore, it seems that clinically there is no difference between the antirachitic effect of vitamin D_2 and that of vitamin D_3.

DR. HENRY J. GERSTENBERGER, Cleveland: I think Dr. Tisdall is right in pointing out that it would be a mistake for any one to infer that in all of the infants that my colleagues and I have protected against rickets the disease would have developed had they not received the parenteral administration of vitamin D_3; however, inasmuch as Cleveland has much less sunshine than Toronto—not because there is so much smoke there but because the frequent cloudy skies make it the poorest in sunlight of the large cities in the United States—and Dr. Tisdall has found that in approximately 50 per cent of the controls rickets did not develop, it seems safe to assume that this percentage would be reduced to 25 or less in Cleveland. In other words, it seems justifiable to maintain that in at least 75 per cent of the children treated in this series rickets would have developed had the protective agent not been used, provided, of course, that they did not receive other antirachitic substances, such as cod liver oil.

I should also like to recall to Dr. Tisdall that because we requested the mothers to give us written permission to attempt to protect their infants against rickets in the manner described, it was impossible for us to alternate patients as controls. Under the circumstances, we felt that we had to trust to luck which, fortunately, turned out to be good, inasmuch as 10 patients with active rickets and 3 with active spasmophilia came under our observation during different weeks of the period beginning with November 1940 and ending with April 1941. The results for these controls, together with those for the patients with rickets whom we treated in the hospital by the parenteral method (with doses of 25,000 or 12,500 U. S. P. units) and observed for a period of at least twenty weeks thereafter, can be accepted as ample.

Dr. Kramer, I know the papers about which you speak; I was responsible for one of them. However, while I did make the statement that on the basis of the data obtained for the small number of rachitic infants there was no practical difference in the antirachitic efficacy of the two milks used (cow's milk which was made antirachitic by irradiation [vitamin D_3] on the one hand and by feeding the cows irradiated yeast [vitamin D_2] on the other), I took the precaution to point out that if there was actually a superiority in the antirachitic effectiveness of the one milk over the other it existed in favor of the irradiated milk (vitamin D_3). In connection with this point, I should like to remind Dr. Kramer that in my introductory remarks I took occasion to emphasize the great advantage of the method we used, in which rachitic (sunlight-deficient) monkeys were employed to determine the relative effectiveness of vitamin D_2 and vitamin D_3, over plans and methods using human material, inasmuch as it was possible for us in that particular study, first, to use two groups of 15 "standardized" rachitic monkeys each and, second, to administer a dose (2,400 U. S. P. units) which was large enough to bring about healing changes, in both the blood and the bones, but small enough to prevent the healing from proceeding too far or to too marked a degree; in other words, our scheme, in which rachitic monkeys were used, prevented the covering up of differences in effectiveness between vitamin D_2 and that of vitamin D_3 by employing too large doses, as some investigators have done. It is difficult to understand how any one can doubt the superiority of vitamin D_3 over vitamin D_2 after having seen the slides which I presented this evening illustrating our results with the rachitic monkeys. I am of the opinion that the same difference could be shown to exist for human beings, if it were possible to study an equal number of infants with rickets of comparable degree.

Final Session

Saturday Morning, May 24

Nine Years' Observation of a Patient with Primary Essential Xanthomatosis. Dr. Béla Schick and Dr. Warren M. Sperry (by invitation), New York.

The history and clinical picture are given. At the age of 4 years the patient was found to have lipemic serum. At this age also cutaneous manifestations appeared. They are now widespread at the elbows, knees, hips, gluteal region and knuckles of the fingers, and around the achilles tendons, where large pendulous tumors are present. The outstanding feature is the marked "arcus senilis" of the corneas.

Thyroid, insulin and lipocaic were tried besides a diet free of or low in cholesterol, with very questionable therapeutic effect. During the last two years the yellow color has become paler. The patient has no signs of arteriosclerosis.

In the beginning the figures for the cholesterol in the serum were above 900. Owing possibly to the influence of the diet, they became lower, between 700 and 800.

The father and mother and one brother had high figures for cholesterol, the father between 350 and 500. In 1934 the youngest brother was normal (cholesterol, 160 mg. per hundred cubic centimeters of blood). Since 1937 his cholesterol has risen to about 350 to 400 mg. No symptoms of xanthomatosis were seen in the parents or brothers.

Three tumors on the knuckles were removed and showed cholesterol to be 14.5 per cent of the dry weight.

The pathogenesis of the disease in this patient is discussed. A disturbance of the vitamin A metabolism may be considered, as the yellow color of the tumors is due to carotene.

DISCUSSION

DR. DONOVAN J. MCCUNE, New York: Dr. Schick has mentioned that although many of these cases exhibit similar clinical features, they are not all identical with respect to the pathogenesis of xanthomatosis. It may be of interest in this connection to recount briefly an experience that my associates and I had about five years ago. The patient was a 6 week old infant who entered the hospital with intense jaundice, which we believed to be due to congenital atresia of the bile ducts. Surgical operation was performed. At operation, although the surgeon identified an underdeveloped extrahepatic biliary system, a needle inserted into what was thought to be the common duct obtained only a small amount of colorless mucoid fluid. Accordingly, congenital atresia of the bile duct was considered to have been established, and the parents were told—with what in retrospect proved to be undue emphasis and assurance—that the child would die. This annoyed the parents, and they, as did the parents of Dr. Schick's patient, became prejudiced against medical science.

Their optimism was borne out when in the outpatient department about two months after operation on the child the jaundice was noted to be conspicuously less. The clinic physician was not much excited by this finding, and the parents were not asked to bring the child for further study.

They did bring the child back, however, at the age of 17 months, entirely free from jaundice and normal in all superficial respects of growth and development but exhibiting the dramatic finding of generalized cholesterosis of the skin, similar in character to that which Dr. Schick's patient showed, but somewhat more diffused; the lesions were all white and pearly looking and, to my considerable interest, seemed to have been intensified at sites of trauma. The surgical incision was marked by a line of cholesterol, and the site of the retention sutures was also so distinguished.

We made several brief observations of the patient, the most outstanding of which was that the serum cholesterol varied between 881 and 1,491 mg. per hundred cubic centimeters. The ratio between combined and free cholesterol was much reduced, varying between 0.06 and 1.06.

Because of the parental prejudice against medical science, we were unable to make observations on their serum cholesterol, so I have no reason to feel that this was a familial disease. It appears more probable that the child had something which for purposes of brevity we may call hepatitis and which exercised a selectively deleterious effect on the liver; this syndrome of what looked to be essential xanthomatosis resulted.

We were able to follow the child for only eight months, and both the father and the mother stoutly withstood all solicitation to have the child admitted to the hospital. He was seen last when 3 years old and appeared to be progressing normally in all respects except for the persistent presence of the cutaneous stigmas of cholesterosis.

DR. JULIAN D. BOYD, Iowa City: About two years ago a normal-appearing 6 month old infant was brought to the hospital from an orphanage because the blood serum obtained for the routine Wassermann test had been milky. A fat content of 15 per cent (15,000 mg. per hundred cubic centimeters) was found, with elevation of all lipids, preponderantly of free fat. The child has been observed during intermittent periods of hospitalization for two years, and marked lipemia persisted until through a low fat diet the lipid content of the blood was reduced to about a tenth of its initial value. The patient has not been ill in any way. Her rate of growth and of development has been as would be predicted for a normal child. The only apparent evidences of her abnormality were a few xanthelasmic lesions on the forearm, the nature of which was confirmed through biopsy.

DR. BÉLA SCHICK, New York: We have several times examined the interns in the laboratory, and once in a while we find somebody who has high cholesterol, sometimes as high as 500 mg. per hundred cubic centimeters. I think there is

some danger that persons of this type will later have clinical symptoms related to such findings. It will be interesting to examine also distant relatives of the patient.

It is hard to get the tumors away from the tendon. It looks easy; the growths look pendulum-like. One tumor could not be removed entirely.

The Premenstrual Vaginal State in Girls. Dr. J. D. Pilcher and Dr. Henry R. Tuchewicz (by invitation), Cleveland.

At a clinic for gonorrheal genital infections in young girls a vaginal condition that has worried a number of mothers and puzzled physicians and nurses has been recognized, a description of which has not been found in writing in English. The young girls have been brought to the dispensary because of a vaginal discharge, often considerable in amount and irritating. Gonorrheal infection was often suspected even by physicians. The exudate in clean patients was distinctly white, not yellow as that from bacterial vaginal infections or that from the presence of foreign bodies in the vagina; in the unclean, it was occasionally dried about the vulva. The tissues of the hymen ring were swollen, soft and of a slightly grayish color. The vaginal reaction was acid to methyl red, i. e., with a p_H from 5.8 to a considerably higher degree of acidity; superficial ulceration had occurred in 2 girls, probably from the high degree of acidity, as the ulcers were cured by cleanliness and alkaline dusting powder. Aside from the exudation, the vagina and cervix seemed normal for the age. The smear showed chiefly large squamous cells, with a varying number of pus cells, occasionally practically none of the latter; a gram-positive flora, more often large rods (lactobacilli) or cocci (enterococci), less often short rods (colon bacilli) or occasionally diphtheroids or any combination of these, was found. Smears made from exudate on the vulva often showed the cells to be shriveled as if old or dried. This is the vulval and vaginal picture that usually follows administration of estrogenic substance to young girls. A number of girls knew approximately when the physiologic change began—11 years 4 months, with extremes of 10 years 4 months and 12 years 8 months; no doubt it occurred earlier. A larger number were unaware of the condition. The mean age at which it was first seen was about 11 years, with extremes of 8 years 6 months and 13 years 5 months. The vulval and vaginal change may be practically complete in eight to ten days, as was noted in 3 girls in the hospital. These girls menstruated seven, eight and fifteen months later. The interval between the appearance of this state and menstruation varied from seven or eight months to two years.

The use of estrogen did not seem to bring about earlier menstruation, although the estrogenic effect may lead directly into the premenstrual state.

Criteria of Recovery After Acute Disease of the Central Nervous System. Dr. Bronson Crothers and Elizabeth Lord, Ph.D. (by invitation), Boston.

Prognosis after an injury or an infection involving the brain in a child is difficult and inaccurate at best, but it is hopelessly inadequate if growth and development are not considered and if recovery is not defined. In this paper conclusions are reported which are based on repeated physical and psychologic appraisals of children who have been seen in a general children's hospital during a period of many years.

In dealing with young adults it is relatively easy to find out the previous status and to appraise recovery, physical, mental and emotional. The essence of recovery in an adult is the restitution of the subject to an already achieved level of competence. Among older persons one demands only that no acceleration of senility take place.

In the case of a child, however, it is necessary to set up a curve of growth against which progress can be charted. It is obvious, of course, that mere restitution to the previous state is arrested development. It is equally important to realize the difficulties which spring up when deceleration of growth or irregularities in elaboration of mental processes occur.

The problem is certainly complex, but it seems clear that it is not completely insoluble. In view of the admitted seriousness of the problems of so-called post-encephalitic and post-traumatic behavior disorders, it is reasonable to explore all possible approaches. This paper is a report of efforts to establish facts about the status before the illness or accident by a careful history of development. Next a rigid appraisal of the damage and psychologic and physical reappraisals at intervals are reported.

With this information in hand, it is possible to establish tentative criteria for recovery.

DISCUSSION

DR. ALFRED H. WASHBURN, Denver: I do not mean to differ with Dr. Crothers as to his essential thesis, with which I have a great deal of sympathy, but I am a little distressed over the apparent implication in the slides of a straight line relationship between chronologic age and mental age. I am not sure that Dr. Crothers intended to imply that there is in the individual child any such straight line relationship, but it seems to me that was the implication in the slide, and it seems to me that is an implication that should be denied.

I wonder if Dr. Crothers would state whether he has made as concentrated studies in following both the intelligence quotient and the behavior of average healthy children as he has made of these abnormal ones.

(Showing Dr. Crothers' last slide) The straight line relationship here, assuming that the child had a similar chronologic age and mental age, is not my experience in following a group of healthy children. In fact, each child has a characteristic pattern of mental growth just as he has of physical growth. They are not all the same, but there are similarities; there is, for instance, frequently a tendency of the mental age to slow off in the preschool years and then to swing up very much the way that one swung up that went to an intelligence quotient of 125.

Further evidence in support of the soundness of the curves of mental growth which my associates and I have relied on is the fact that these curves show the same sort of break in the preadolescent period that appears in curves of physical growth. There is also a nice correlation in the intervals of time between the menarche and the breaks in the mental and physical growth curves, so that all in all we feel we are getting adequate pictures of mental growth curves, and they are by no means straight line relationships.

As I say, I do not want to disagree with Dr. Crothers as to the essential thesis, but I do think pediatricians should try to get in their minds the picture of the mental growth curve as a thing characteristic for the individual child and that in interpreting an apparently abnormal curve they should remember the tremendous amount of variation in the individual's mental growth curve.

DR. ELIZABETH LORD, Boston: I am very grateful for that clear presentation of a point of view. We used that line to represent time in relation to characteristic items of behavior, such as were standardized by Dr. Gesell and such as one finds in the Stanford-Binet scale. We use the mental age only as an objective score for summing up mental development. It is a crude measure, but as a mental age score it can be plotted. I hope that those slides do give you an impression of what we mean by return of function and the length of time which may elapse before there is a return of adequate mental progress.

Actually, the more interesting and more convincing material comes from the incidental observations—from the special types of tests, the sensory-motor tests, from our efforts to teach and from the appraisal of the results of teaching by the public school teachers. We make an effort to appraise rather subjectively the decrease in hyperactivity that the children show and the return of mental strength, on which concentration and purposefulness depend. These observations are the points around which we feel that the child shows mental inadequacy or adequacy, and it is these supplementary observations which are not open to charting but which give the most convincing evidence of prolonged convalescence.

DR. BRONSON CROTHERS, Boston: I recognize, of course, that the method of charting is open to challenge. We wish to emphasize, first, that it is necessary to collect information about the child as it was before the accident or the onset of disease, information which would justify prediction about his expected development. It is necessary to follow the child long enough to establish the probability that he is progressing along the predicted course. We believe that charting against a straight line, to which Dr. Washburn takes exception, illustrates our point, though, of course, it cannot be regarded as a proper way of dealing with many developmental problems.

DR. ELIZABETH LORD, Boston: I think I agree entirely with Dr. Washburn: In other words, individual variations on the tests suggest that children do have their own individual and variable rates. What I wanted to bring out on the charts is that in addition to the summation of the mental age we have the special information from sensory-motor tests, the lack of concentration and the difficulties in learning, which are quite aside from the summing up of the mental age, but by graphing the crude score of mental age we try to get into a picture form, so to speak, the long delay before there is a return of function and the adequate mental gain which makes it possible for the child to progress year by year in school comfortably and easily. Supplementary tests often reveal the disabilities and help us when we are interpreting the behavior to the family, as well as help the teacher to protect the child from overstress.

Chronic Acidosis as a Concomitant of Late Rickets. DR. JULIAN D. BOYD and GENEVIEVE STEARNS, PH.D. (by invitation), Iowa City.

Chronic acidosis has been present in half of the patients with late rickets studied at the University of Iowa. The existence of acidosis was not apparent from symptoms but was demonstrable through estimation of the alkali reserve and analogous biochemical analyses. It is believed that both the acidosis and the disturbance of bone structure were dependent on the breakdown of normal patterns of electrolyte metabolism, distinct from those operative in infantile rickets and in certain other forms of late rickets. It seems probable that late rickets may result from a prolonged deficit in base which, if not adequately compensated, leads to depletion of calcium and to alteration of the mechanisms for the elimination of water and electrolytes. In 1 child, evidences of rickets and of deficit in base were present even though the alkali reserve remained normal. In 2 patients, healing of rickets and of associated osteoporosis was obtained through prolonged and continued administration of alkali. Through such medication, certain biochemical constituents of the blood were restored to normal levels and tended to remain at the normal levels as long as alkali therapy was continued. In all subjects in the series there were evidences of perversion of certain phases of renal function, but in several this was not dependent on any detectable disease of the kidney itself, and the pattern of disturbance was dissimilar from that usually implied by the term "renal insufficiency." It seems likely that the evidences of renal dysfunction were reflections of disturbances of balance in the extracellular fluids rather than of an intrinsic inability of the kidney to function normally.

On the basis of the observations cited, we feel that with chronic acidosis of any cause the maintenance dosage of alkali should be employed to avoid depletion of base. In some patients who have experienced such depletion, with development of lesions of bone, administration of an alkali has relieved all noteworthy clinical evidences of disturbance. In others (e. g., those with chronic azotemic renal insufficiency) the alkali therapy has been well tolerated, even for years, and has served to alleviate some of the clinical symptoms.

To illustrate the effect of alkali therapy, the authors cite the record of an 11 year old girl with low alkali reserve, hypochloremia, polyuria, inability to secrete acid urine and active rickets. The differentiation of the findings in this instance from those of Fanconi's syndrome and those of azotemic renal insufficiency is offered.

DISCUSSION

DR. GEORGE M. GUEST, Cincinnati: I should like to offer some speculations concerning disturbances in phosphorus metabolism which may accompany conditions such as those studied by Dr. Boyd—disturbances which may be intimately concerned with the electrolyte disequilibrium in the body fluids to which he has referred. Acidosis due to many different causes is known to be accompanied by excessive phosphaturia. This was noted in diabetic acidosis in 1900 by Von Noorden. In 1924 Haldane and co-workers demonstrated that ammonium chloride acidosis was associated with excessive phosphaturia and a greatly reduced concentration of organic acid-soluble phosphorus in the blood cells. Haldane insisted that some of the ill effects of acidosis might be due to a depletion of labile phosphorus reserves (compounds in blood cells and soft tissues) resulting from phosphaturia. The significance of the organic acid, soluble phosphorus compounds of the blood cells in relation to the electrolyte equilibrium of the blood has been dealt with in a series of papers from our laboratory in Cincinnati. In diabetic acidosis there occurs a great reduction of total base in the blood (both plasma and cells), which can be explained as partly due to excretion of base with phosphates in the urine. Impairment of renal function may be accompanied by a lessened ability to use ammonia formation or phosphate buffering to conserve base. Since depletion of base in itself contributes to the development of acidosis, a vicious cycle can be readily visualized. Since excessive phosphaturia is likely to occur even in mild acidosis, a long-continued drain of phosphorus from the body may be an important factor in the development of or persistence of late rickets in patients such as those described by Dr. Boyd and others as suffering from chronic acidosis of undetermined origin.

DR. SAMUEL Z. LEVINE, New York: Dr. Harrison has shown that one of the functions of vitamin D in ordinary rickets is to increase the tubular resorption of phosphate and to increase the inorganic phosphate of the blood serum. He also showed that administration of parathyroid or ammonium chloride affects the tubular resorption of inorganic phosphate.

The possibility that the type of rickets under consideration is refractory to the administration of vitamin D exists in that tubular resorption of phosphate is not made effective by the administration of vitamin D. I wonder whether it would not be worth while to do phosphate clearance tests in these youngsters in order to demonstrate whether there is some fundamental defect in tubular resorption of phosphate.

DR. DONOVAN J. MCCUNE, New York: I think that Dr. Levine's suggestion is highly relevant to the interpretation of this type of case. Parenthetically, I may state that we have just completed a series of simultaneous endogenous creatinine and phosphate clearance studies on 2 patients with refractory rickets of the type which responds only to extraordinarily large amounts of vitamin D. Those who are interested in this matter will perhaps wish to know that these studies show what appears to be a normal clearance of phosphate.

It seems to me that a good many cases of so-called metabolic rickets are most readily interpreted on the assumption that, although they are clearly not examples of classic renal rickets, they are none the less due to renal disease—not to a disturbance of glomerular filtration but to a defect of tubular function. I see affirmative nods; hence I shall not go into the evidence which leads to this statement. Certainly in the type of rickets to which Fanconi directed so much attention in the species of hypophosphatemic, hyperchloremic rickets which Albright described and in which a cure was accomplished with sodium citrate-citric acid mixtures combined with vitamin D, as well as in certain other varieties, the most reasonable assumption is that one or another of the complicated set of functions performed by the renal tubules is specifically and in a measure selectively disturbed.

It occurs to me to suggest that in Dr. Boyd's case the lesion probably consisted in defective resorption of sodium from the glomerular filtrate. When adequate amounts of sodium were rendered available therapeutically, it became possible to maintain an adequate blood concentration of this action, with the

consequence that other alterations in the composition of the blood plasma which were secondary to the acidosis due to sodium depletion were reversed and healing of rickets rendered possible.

It appears that one of the most important manifestations of lesion in the Fanconi syndrome is defective tubular resorption of phosphate. I depend rather heavily for that statement on the evidence supplied by Dr. Harriet Guild some years ago in a statement to the effect that efforts to treat a patient with Fanconi rickets by generous doses of sodium led only to drowsiness and collapse and were not remedial. The experience has been duplicated less clearly by others in attempts to treat patients for Fanconi rickets.

If it be true that defective tubular resorption of phosphate is an important element in the pathogenesis of the Fanconi syndrome, then it is rational to attempt treatment not by the administration of the cation sodium but by the use of substantial amounts of phosphate. The recent publication of Gittleman and Pincus lends some admittedly insubstantial support to the possibility of benefit from this type of procedure.

DR. BENJAMIN KRAMER, Brooklyn: I should like to ask a few questions. I did not see any statement as to what the fixed base concentration in the plasma was in this case. If the total fixed base concentration was reduced to conform to the reduction of bicarbonate, chloride and phosphate, there must have been a considerable decrease of the total electrolyte concentration of the serum and hence a marked disturbance of the osmotic equilibrium.

It would also be interesting to know the total amount of organic acid excreted in the urine and the amount of undetermined acid in the blood.

DR. HARRY H. GORDON, New York: I think that Dr. Boyd has presented specific evidence of a tubular defect in this patient in whom in addition to rickets there were fixed specific gravity of the urine and polyuria and in whom the administration of pitressin caused no increase in concentration of the urine. Sodeman and Engelhardt have recently presented evidence that in both normal persons and in patients with renal disease the response to pitressin followed closely the results of the ordinary concentration tests in which the fluid intake is restricted. This failure to concentrate the urine after the administration of pitressin might then be considered as a disturbance in the ability of the renal tubule to reabsorb water. As suggested by Smith and his co-workers, this defect may lie in the distal portion of the tubule.

DR. JAMES L. GAMBLE, Boston: The many interesting implications of this situation as regards acid base metabolism and renal physiology have been pretty well indicated. I am especially entertained by the bare fact that this child was not able to secrete acid urine. I never had the luck to encounter a person who could not secrete acid urine. This being so, I wonder why there was not a larger increase in the production of ammonia to compensate for this inability to conserve base by secreting acid urine.

The production of ammonia, however, is a very rough and slow-going adjustment. The last and fine adjustment of the mechanism conserving fixed base is accomplished by an alert regulation of the acidity of the urine. So it may be that the ammonia mechanism by itself is not nearly accurate enough to prevent a loss of fixed base. Dr. Boyd's interpretation of his findings from the point of view of therapy seems to me sound.

DR. JULIAN D. BOYD, Iowa City: Our record of this patient's metabolic status is incomplete in some regards, so that we cannot reconstruct the whole picture without making certain assumptions. Phosphorus partition studies of the blood were made, including the composition of the erythrocytes, and have been published in connection with another report (Stearns, G., and Warweg, E.: Studies of Phosphorus of Blood: III. The Phosphorus Partition in Whole Blood and in Serum and the Serum Calcium and Plasma Phosphatase During Healing of Late Rickets, AM. J. DIS. CHILD. **49**:79 [Jan.] 1935). The levels of inorganic phosphorus in the serum and of ester phosphorus in the cells were notably reduced. The amount of phosphorus excreted in the urine was within normal limits, and

during the first period of observation the loss of calcium far outweighed the loss of phosphorus. The phosphorus balance and the blood levels of inorganic phosphorus and of ester phosphorus were restored so promptly through therapy that depletion of phosphorus seems unlikely as an explanation of this patient's condition.

There seems little reason to doubt that tubular dysfunction played an important role in this patient's status. Judgment is reserved, however, as to whether the derangement was not functional rather than representative of a defect of the kidneys whereby they were unable to function normally. It is true that apparent normality of cellular structure at the time of autopsy does not establish physiologic integrity of the tissue during life. On the other hand, it is known that renal dysfunction may arise secondary to extrarenal conditions and cause the observer to conclude that renal disease is present, yet through correction of the extrarenal abnormality normal renal function may be resumed. I have in mind a patient with hyperparathyroidism whose apparent evidences of renal disease disappeared following removal of a parathyroid adenoma.

The excretion of ammonia by the child with chronic acidosis was similar in degree to that by the normal nonacidotic child: about 20 milliequivalents each day. During administration of an alkali this was reduced by about 40 per cent. The ammonia output was not as great as one would expect from a subject with chronic acidosis. Whether this reduction represents an inability to form ammonia as a measure for conservation of fixed base, or whether it is determined by the enforced excretion of neutral urine, is a question we have not been able to answer.

Amino Acid Studies in Nephrosis. Dr. John D. Lyttle, Dr. Elvira Goettsch (by invitation) and Dr. David McLean Greeley (by invitation), New York.

Weech and others have demonstrated morphologic changes in the liver in hypoproteinemic dogs. We have studied the manner in which the plasma amino acids are cleared following an injection of casein hydrolysate in hypoproteinemic patients and dogs. In hypoproteinemic dogs there was a definite delay in clearing the blood of amino acids. The retention of plasma amino acids was evident after only one week of the low protein diet and increased as hypoproteinemia progressed. Since marked morphologic change was demonstrated in the liver and relatively little in the kidney of the dog, it was assumed as a working hypothesis that the retention was probably caused for the most part by hepatic injury.

Casein hydrolysate was injected intravenously into 7 normal children in the hospital who had no clinical evidence of hepatic or renal disease. Blood was taken before and at intervals after the injection. After a variable initial rise, which occurred five minutes after the injection, there was a rapid fall in plasma amino acids. The preinjection level was reached in thirty-five minutes in 3 children and in ninety-five minutes in all of the children.

The same procedure was carried out with children who had nephrosis. Repeated curves for 2 children and single ones for the other patients gave results that were quite similar to those for the control group. Although hypoproteinemia is severe in nephrotic children, they show no impairment in ability to clear the blood of amino acids after an intravenous injection of casein hydrolysate.

For comparison, tests were made on children in the nephrotic stage of chronic glomerular nephritis. All of these children had enlargement of the liver and impairment of renal function. After the injection of casein hydrolysate, the initial rise of plasma amino acid nitrogen was much higher than in the control and nephrotic groups, and a marked retention of amino acids occurred. There seemed to be no relation between these findings and the degree of renal insufficiency.

Tests were carried out on 2 children with portal cirrhosis. In both of these children renal function as determined by the urea clearance test was normal. The two curves were quite different from those of the control series in that both showed a delay in the clearing of the blood of amino acids after the injection of casein hydrolysate.

Although the series is small, certain conclusions may be hazarded: Retention of plasma amino acids after an intravenous injection of casein hydrolysate occurs in hypoproteinemic dogs but not in patients in the active stage of nephrosis with marked hypoproteinemia and unimpaired renal function. Marked retention occurred in 2 patients with portal cirrhosis and in 3 patients in the nephrotic stage of chronic glomerular nephritis with hepatomegaly. It seems probable that the retention is caused by hepatic injury.

A Comparison of the Routine Urinalysis, the Addis Count and the Blood Sedimentation Rate as Criteria of Activity in Acute Glomerulonephritis. Dr. Mitchell I. Rubin, Dr. Milton Rapoport (by invitation) and Dr. Arthur D. Waltz (by invitation), Philadelphia.

In a series of 40 patients with acute glomerulonephritis, hospitalized during the entire period of their observation, the average time of recovery as based on each of criteria mentioned in the title as follows: (1) return of the routine urinalysis to normal, thirty-seven days; (2) return of the Addis count to normal, one hundred and twenty days; (3) return of the sedimentation rate to normal, eighty-six days.

There was a close correlation between the length of time it took the sedimentation rate to return to normal (eighty-six days) and the interval of time required for the number of red cells in the Addis count to fall below 10,000,000 (seventy-six days). In almost all cases in which the red cells in the Addis count fell below 10,000,000 and in which no intercurrent infection supervened, complete recovery (normal Addis count) followed soon afterward.

In patients in whom the Addis count and the sedimentation rate were showing progressive improvement, the occurrence of an intercurrent infection (usually of the upper respiratory tract) reversed the trend of both for a period of at least two months.

In only 3 instances did the Addis count return to normal before the sedimentation rate.

In cases of chronic nephritis, the sedimentation rate is persistently rapid.

From our data it is justifiable to conclude that the sedimentation rate may be used as a criterion of activity and recovery in acute glomerulonephritis. We have encountered but one exception to this.

DISCUSSION

Dr. John D. Lyttle, New York: Studies in our clinic corroborate Dr. Rubin's report of the close relation between the sedimentation rate and the activity of nephritis. We have used this rate as an objective guide in regulating the activity of the patient in convalescence.

Without a careful analysis of our data I should not like to say there is always agreement between the sedimentation rate and hematuria. The sedimentation rates of some of our children with severe infection and mild nephritis remained high for some time after the nephritis had healed and hematuria had entirely disappeared. This is to say that I think the sedimentation rate is more likely to reflect the severity of the infection than the severity of the nephritis.

I admit that many routine urinalyses are worthless in the attempt to determine the presence or absence of mild degrees of renal damage. In our experience this can be done by careful routine urinalysis—that is, repeated examinations of concentrated urine. We have not felt that the expensive, time-consuming Addis count is of any more help in answering the question than a carefully done urinalysis.

Dr. Béla Schick, New York: Dr. Rubin asked me what I think about sensitization. Any one with a theory likes to hear that his theory is correct. I think as far as disease is concerned that the sensitization comes during the disease. I am very reluctant to accept a specific sensitization only with streptococci. The presence of sensitization could be easier proved if the first part of the disease

had already finished its course when the new attack came about. This second attack would then have appeared without an incubation period.

DR. MITCHELL I. RUBIN, Philadelphia: In answer to Dr. Lyttle's remarks, we certainly do not believe the routine urinalysis should be discarded, for much can be learned from it. We should like to emphasize, however, that on a day when routine examination shows the urine free of red cells, the Addis count may show up to 30,000,000 red cells. In other words, for the estimation of return to normal after an acute attack of glomerulonephritis the routine urinalysis is not accurate enough.

Regarding Dr. Lyttle's remarks on the sedimentation rate, I again would like to emphasize the long time it takes for the average sedimentation rate to become normal—in the average case, about three months, which is much longer than the time taken for the return to normal in a child with an acute infection of the upper respiratory tract and no nephritis. Again, in patients with chronic nephritis in whom no infection of the respiratory tract can be found, the sedimentation rate remains constantly rapid.

A Further Attempt to Describe Volume Changes in Body Fluid. DR. JAMES L. GAMBLE, Boston.

The calculation of change in volume of extracellular fluid from measurements of change in sodium balance is satisfactorily approximate under ordinary circumstances. When, however, there is a large difference in tonicity between the water sodium chloride intake and the body fluids, the transfer of water between extracellular and intracellular fluid and the change of some degree in the concentration of total electrolyte must, as shown by Darrow and Yannet, be taken into account, together with a change in balance of the intracellular base potassium. Data are presented which illustrate body fluid volume changes in the presence of these several variables.

DISCUSSION

DR. A. ASHLEY WEECH, New York: Dr. Gamble, I am delighted by the simplicity of your mathematical logic. I remember some years ago making a careful study of the metabolism of several dogs during the formation and delivery of edema. The diet, the stools and the urine were analyzed for sodium and for chloride. Finally the balances were used to calculate the losses and gains of extracellular fluid. And then it was found that these losses and gains checked closely with the changes in body weight. In other words, the labor of months of analytic work could have been saved by computing the sodium and chloride balances from the shifts in body weight. I was greatly chastened by the experience.

Loneliness of Infants. DR. HARRY BAKWIN, New York.

The failure of infants to thrive in hospitals is one of the most obscure phenomena in pediatrics. Until the early years of this century, the high institutional death rate was attributed to nutritional disturbances. During more recent years, emphasis has shifted to infection as the offending mechanism. In an effort to prevent hospital cross infections more and more rigid isolation is being advocated.

It is the purpose of the present communication to point out, from analogy with the mammalian world, the need of the young infant for social stimulation and the deleterious effects of isolation in an institution on growth and development. Various methods aimed at humanizing the care of infants in hospitals are advocated.

DISCUSSION

DR. FRANCIS SCOTT SMYTH, San Francisco: I just want to say I think Dr. Bakwin would thoroughly approve of the system in the Children's Hospital in Buenos Aires, Argentina, where the mothers and newly born infants are kept

together, and mothers are allowed to assist with the nursing care of their infants and children. Provisions are made for the mothers to stay in the hospital. Even in the Pavilion for Children with Contagious Diseases there is a very large glass window through which parents can see their children at any time. I rather suspect, however, that our Latin colleagues are more concerned, perhaps, with maternal loneliness.

DR. FRITZ B. TALBOT, Boston: I think Dr. Bakwin's subject is very timely. I remember that twenty-eight years ago in Düsseldorf, Germany, I made a visit to a hospital, and there was a very fat old lady wandering around the ward with a baby on her hip, a very measly baby. I asked Schlossmann what she was doing with the baby, and he said that whenever he had a baby for whom he and his associates had done everything they knew how to do medically and were unsuccessful, he gave the baby to Old Anna and told her to take it in charge, and that Old Anna was always successful. In other words, Old Anna mothered these babies.

I do not think that this psychologic attack on the problem should be confined to babies only. For years in our childrens' service at the Massachusetts General Hospital we have had what the children called a "play lady" whose one job is to do the same thing for the children. I agree heartily with what Dr. Bakwin has said. I believe such provision does reduce the length of stay in the hospital for both babies and children, and that it makes the results of the medical treatment much more effective in children of all ages.

DR. SAMUEL Z. LEVINE, New York: I should like to cite an instance corroborating the experience that Dr. Bakwin has had. We have at the New York Nursery and Childs Hospital and the New York Hospital a metabolism unit in which we have three to four nurses to every infant. Whenever an infant does not do well in the wards and suffers from severe malnutrition or marasmus, and we cannot do anything medically to help him, we transfer the youngster to the metabolism unit, and almost invariably, without other changes, the infants do remarkably well. I think it is due entirely to the fact that there are four nurses assigned to each infant, so that they have time to play with the youngsters.

DR. HARRY BAKWIN, New York: I think we ought to consider seriously whether we are giving proper attention to the psychologic needs of the newborn baby when we isolate it from the mother as is common practice at present. Certainly, separation of mother and offspring is not customary behavior among mammals. We have gone to the animal world for much of present knowledge of human physiology. It is reasonable that we should consult animal behavior in the study of the springs of human behavior.

Book Reviews

Age Morphology of Primary Tubercles. By Henry C. Sweany, M.D., Medical Director of Research, City of Chicago Municipal Tuberculosis Sanitarium, and Research Associate, University of Chicago. Price, cloth, $5.00. Pp. 265, with 72 plates and 26 charts. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

In a beautifully illustrated monograph, Sweany has traced the course of tuberculous disease in the body and has made a definite contribution concerning the pathogenesis of tuberculous lesions, with particular reference to primary tubercles. The author himself calls attention to the fact that the results of his study may be applied most suitably to work with patients who have active tuberculosis or to postmortem study in cases of the disease which terminate fatally. Such a restriction merely emphasizes the direction for the application of the results; it does not invalidate the conclusions to any important degree. Particularly to be recommended are the methods of postmortem roentgenologic examination of the lungs and of subsequent gross and microscopic study. A useful, and apparently new, method of recording in schematic form the important data concerning the contact and the clinical histories is used throughout the factual portion of the text. Only about 20 per cent of primary tubercles could be recognized roentgenologically during life. The one conclusion of prognostic value appears to be the generalization that any lesion which is large and not well calcified is potentially dangerous.

The book must be read in detail by the interested pathologist, roentgenologist, pediatrician or internist. If no conclusion warranting a complete change in present conceptions of the pathogenesis of tuberculosis has come out of this study, it can be said, at least, that older conceptions have been better documented than ever before and that some new ideas which are provocative and capable of stimulating new work are contained in this monograph.

The author and the publisher are to be congratulated on the excellence of the illustrations and on the pleasing format.

The Heart in Pregnancy and the Childbearing Age. By B. E. Hamilton and K. Jefferson Thomson. With a section entitled "Delivery and Obstetrical After-Care of Cardiacs," by Frederick C. Irving. Price, $5.00. Pp. 402, with 31 illustrations. Boston: Little, Brown & Company, 1941.

The excellence of this monograph is based on the fact that it records the results obtained by a cardiologist, a physiologist and an obstetrician working together in the same clinic over a period of years. The fundamentals of their work are clearly stated, and the most important details are italicized. The improvement in results which the authors report is undoubtedly due to their close cooperation and to the fact that their basic conclusions are drawn from the results obtained in their own cases over many years. The fundamental rules laid down for the selection of patients with cardiac disease will be helpful to practitioners of obstetrics. These rules unquestionably will prevent many patients who do not have true cardiac involvement from being made heart conscious and will, as well, give practitioners a better understanding of prognosis during immediate and future pregnancies in cases of true cardiac involvement.

The statement that an obese patient with cardiac disease is an insufficiently treated patient deserves special attention and probably should be extended to include all obese obstetric patients. The conservative obstetric routine developed by Dr. Irving in his treatment of patients with cardiac disorders illustrates well the good results of applying the carefully controlled, combined efforts of the various departments concerned to the solution of a medical problem.

Natural Resistance and Clinical Medicine. By David Perla, M.D., and Jessie Marmorston, M.D. Price, $10.00. Pp. 1,344, with no illustrations. Boston: Little, Brown & Company, 1941.

This volume of 1,344 pages actually is a reference book and does not lend itself well to abstracting. It should be in the hands of every person who practices progressive medicine or does research.

The scope of the material considered is impressive; fundamental points are included; the conclusions and illustrations are practical. The book is a survey of natural immunity. It is complete and covers the subjects of heredity, age, sex, the endocrine glands, the humoral and cellular mechanisms, the liver, the body surface and the nervous system, states of impaired health caused by dietary deficiencies and climate in their relation to resistance to disease. The clinical aspects of resistance are likewise considered. Never before have all of these subjects been brought together in this fashion. One can agree with these statements in the circular accompanying the book: "For the first time in modern medicine there is available a complete review of our knowledge of the natural defenses of the body against infections and toxins"; "Almost every phase of the science of the living body—from clinical and experimental medicine to experimental biology and biochemistry—has made its contribution to the more than five thousand papers upon which the authors have drawn."

The volume makes easy reading; the style is simple and clear. This book is a "natural" and should be on the "must" list of every physician.

Science and Seizures. By William G. Lennox, M.D. Price, $2.00. Pp. 258. New York: Harper & Brothers, 1941.

This book supplies in readable form a great many facts about epilepsy and migraine. The literature on these subjects is enormous and must be read and sifted with judgment. Dr. Lennox, because of his wide experience and his long study of these diseases, is eminently suited to select and to evaluate the literature. Consequently, the volume will be of value to the physician, and it will also be interesting and valuable to the intelligent layman or patient, for it answers in relatively simple terms many of the questions which patients ask.

The book includes a timely discussion of the most recent means of studying persons with epilepsy, that is, the electroencephalograph. The use of this instrument has undoubtedly increased the knowledge of what transpires in the brain during epileptiform attacks, but it is worthy of note that Dr. Lennox points out that "the value [of the information obtained] is more scientific than practical." It is to be hoped that in time such data will also have more practical importance.

As is noted in the introduction, "Science and Seizures" is not intended as a manual of self treatment. It contains no detailed outline of therapy, for this may be obtained from textbooks. There are timely remarks on the use of patent medicines and on the relative costs of such medicines and the commonly used drugs.

The book can be recommended to the physician without reserve.

Biology of the Laboratory Mouse. Edited by G. D. Snell. Price, $7.00. Pp. 497, with 170 illustrations. Philadelphia: The Blakiston Company, 1941.

The articles in this book have been contributed by the staff of the Roscoe B. Jackson Memorial Laboratory, with the collaboration of Dr. J. H. Dingle, of the Harvard Medical School. Each chapter has been written by an authority, who has gathered from a rather diffuse literature the established facts regarding his subject and has presented them in a concise, clear form. The book has been written principally for the busy research worker who uses or desires to use mice as experimental material. Since the mouse is more widely used than any other animal in research on cancer and in the investigation of genetic and bacteriologic problems, this well conceived and written book with its valuable reference lists is a signal contribution to biologic and medical research.

To the physician the chapters entitled "Gene and Chromosome Mutations," "The Genetics of Spontaneous Tumor Formation," "Endocrine Secretion and Tumor Formation" and "The Milk Influence in Tumor Formation" will prove highly instructive and interesting, for the most recent advances in the fields indicated are so presented that he can become acquainted with them in a relatively short time.

Play for Convalescent Children in Hospitals and at Home. By Anne Marie Smith. Price, $1.60. Pp. 133, with no illustrations. New York: A. S. Barnes & Company, 1941.

Children are taken to hospitals to regain their health; yet all too often their mental health is actually impaired while they are undergoing treatment. A great deal can be done to prevent medical fears in children and to alleviate the harmful effects of hospitalization by play—especially if it is directed by a professionally trained worker. This book outlines the organization, administration and technic of the play program carried out in a large children's hospital. In addition to descriptions of the methods used, there are a complete classification of the forms of play and a list of play materials.

The book is well written by an experienced worker in this new and important field. It should be of great value to hospital administrators, to pediatricians and to nurses who work with children.

News and Comment

GENERAL NEWS

The American Board of Pediatrics.—The lists for the fall examinations are closed. The dates for the examinations in spring 1942 have not been set, but the locations and the approximate dates are as follows: Philadelphia, at the time of the meeting of the American Academy of Pediatrics, Region I, probably in March or April; Cleveland, at the time of the meeting of the American Academy of Pediatrics, Region III, probably in May, and Los Angeles, at the time of the meeting of the American Academy of Pediatrics, Region IV, probably in May.

Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
General Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.
Assistant Secretary-Treasurer: Dr. Charles F. McKhann, University of Michigan, Ann Arbor, Mich.

Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston. Time: Postponed indefinitely.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

British Paediatric Association

President: Prof. Charles McNeil, 44 Heriot Row, Edinburgh, Scotland.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandsche Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaasbolwerk 14ª, Utrecht, Holland.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage, Holland.
Place: Different places. Time: Three times a year.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASE IN CHILDREN

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

SOCIEDAD CUBANA DE PEDIATRÍA

President: Dr. Clemente Inclan Costa, Manrique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Vedado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Jorge Muñoz Turnbull, Av. Alvaro Obregón 186, Mexico, D. F.
Secretary: Dr. Fernando López Clares, Medellín 191, Mexico, D. F.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Ernesto Vizcarrondo, Venezuela.
Secretary: Dr. E. Santos Mendoza, Venezuela.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincaré, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue du Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Conrado Pelfort, Av. 18 de Julio 1246, Montevideo.
Secretary: Dr. Héctor Mourigan, Av. 18 de Julio 2175, Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Philip M. Stimson, 25 Claremont Ave., New York.
Secretary: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Place: Atlantic City.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Richard M. Smith, 66 Commonwealth Ave., Boston.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Statler Hotel, Boston. Time: Oct. 9-11, 1941.
Region I. Place: Philadelphia.
Region III. Place: Hotel Cleveland, Cleveland. Time: May 14-16, 1942.
Region IV. Place: Los Angeles.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Dr. D. L. Richardson, 593 Eddy St., Providence, R. I.
Secretary: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.

American Pediatric Society

President: Dr. Edwards A. Park, Johns Hopkins Hospital, Baltimore, Md.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.

Canadian Society for the Study of Diseases of Children

President: Dr. L. M. Lindsay, 815 Medical Arts Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.
Place: Brockville, Ontario. Time: June 14, 1941.

Society for Pediatric Research

President: Dr. George M. Guest, Children's Hospital, Cincinnati.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Eugene Smith, 385-24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. S. G. Henricke, 4215 N. E. Hancock St., Portland, Ore.
Secretary: Dr. J. S. Backstrand, 333 Wyatt Court, Salem, Ore.
Place: Vancouver, B. C. Time: June 21, 1941.

Rocky Mountain Pediatric Society

President: Dr. Donn Barber, 802½–8th Ave., Greeley, Colo.
Secretary: Dr. Kenneth Schmidt, Republic Bldg., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Harvey F. Garrison, 319 E. Capitol St., Jackson, Miss.
Secretary: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables, Fla.

STATE

Alabama Pediatric Society

President: Dr. M. V. Adams, 803 Government St., Mobile.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. William Belford, 233 A St., San Diego.
Secretary: Dr. John J. Miller Jr., 2398 Sacramento St., San Francisco.

Florida State Pediatric Society

President: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables.
Secretary: Dr. George N. Leonard, 605 Lincoln Rd., Miami Beach.
Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. R. C. McGahee, 1345 Greene St., Augusta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. D. C. Darrow, 789 Howard Ave., New Haven.
Secretary: Dr. Joseph L. Hetzel, 103 N. Main St., Waterbury.
Time: Three meetings a year.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Orville Barbour, 331 Fulton St., Peoria.
Secretary: Dr. Craig Butler, 715 Lake St., Oak Park.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Blvd., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Morgan J. Foster, 837 Higley Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.

Louisiana State Pediatric Society

President: Dr. Julian Graubarth, 3431 Prytania St., New Orleans
Secretary-Treasurer: Dr. W. C. Rivenbark, 3503 Prytania St., New Orleans.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Norman L. Hawkins, 11 Public Sq., Watertown, N. Y.
Secretary: Dr. William J. Orr, 135 Linwood Ave., Buffalo.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.
Secretary: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Place: Pittsburgh. Time: Sept. 29-Oct. 2, 1941.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Harry Towsley, University of Michigan Hospital, Ann Arbor.
Secretary: Dr. Leon DeVel, 110 E. Fulton, Grand Rapids.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. J. C. Iwersen, 236 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. Elmer W. Bantin, 440 Aquila Court Bldg., Omaha.
Place: As announced by Committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Thomas M. Watson, Greenville.
Secretary: Dr. Frederick B. Haar, Greenville.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. Ben H. Nicholson, 301 N. W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. R. B. Josey, 1517 Hampton Ave., Columbia.
Secretary-Treasurer: Dr. Wilson Ball, South Carolina State Health Dept., Columbia.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Secretary: Dr. Gilbert Eblen, 611 W. Main Ave., Knoxville.

TEXAS PEDIATRIC SOCIETY

President: Dr. P. E. Luecke, 4105 Live Oak St., Dallas.
Secretary-Treasurer: Dr. John Ashby, 3610 Fairmount Ave., Dallas.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. John M. Bishop, 511 Medical Arts Bldg., Roanoke.
Secretary: Dr. Edwin A. Harper, 301 Rivermont Ave., Lynchburg.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Theresa O. Snaith, 450 Center Ave., Weston.
Secretary: Dr. Henrietta L. Marquis, 211 Bair Bldg., Beckley.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada.
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. David Greene, 910 Grand Concourse, New York.
Secretary: Dr. F. E. Chick, 2325 University Ave., New York
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. John A. Monfort, 861 Carroll St., Brooklyn.
Secretary: Dr. Walter Coles, 604–2d St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, August and September.

Central New York Pediatric Club

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and September.

Chicago Pediatric Society

President: Dr. James H. Wallace, Chicago.
Secretary: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Dallas Pediatric Society

President: Dr. Edgar Loomis, 351 W. Jefferson Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. Marsh M. Poole, 773 Fisher Bldg., Detroit, Mich.
Secretary: Dr. Donald J. Barnes, 773 Fisher Bldg., Detroit, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Thomas J. Donovan, 3820 Fannin St., Houston, Texas.
Secretary: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. John Aull, 1103 Grand Ave., Kansas City.
Secretary: Dr. George Herrman, 1107 Bryant Bldg., Kansas City.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Alonzo Cass, 1908 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Gladys Patric Shahovitch, 3936 Roderick Rd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Sydney Nussbaum, 247 Ocean View Ave., Brooklyn.
Secretary: Dr. Harry S. Bikoff, 850 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month, October to April, inclusive.

MEDICAL SOCIETY OF THE COUNTY OF QUEENS, INC., SECTION ON PEDIATRICS

Chairman: Dr. A. A. Trivilino, 88-07–150th St., Jamaica, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. Harry A. Ong, 1801 I St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. William F. Burdick, 5402 Connecticut Ave. N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. E. C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. R. P. Schowalter, 411 E. Mason St., Milwaukee.
Secretary-Treasurer: Dr. George H. Wegmann, 2650 W. Hopkins St., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

Chairman: Dr. Leslie O. Ashton, 850 Park Ave., New York.
Secretary: Dr. Alfred Langmann, 108 E. 68th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

NORTHERN CALIFORNIA AFFILIATES

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A. Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. Harold Flanagan, 711 Lowry Medical Arts Bldg., St. Paul, Minn.
Secretary-Treasurer: Dr. George B. Logan, Mayo Clinic, Rochester, Minn.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. J. Byron Snow, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Fourth Friday of each alternate month.

Philadelphia Pediatric Society

President: Dr. Philip S. Barba, 222 W. Harvey St., Germantown, Pa.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

Pittsburgh Pediatric Society

President: Dr. E. L. Piper, 3200–5th Ave., Pittsburgh.
Secretary-Treasurer: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Louise Fry Galvin, 214 S. Boulevard, Richmond, Va.
Secretary-Treasurer: Dr. Herman W. Farber, 501 E. Franklin St., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Herbert Soule, 122 Rutgers St., Rochester, N. Y.
Secretary-Treasurer: Dr. Jerome Glaser, 300 S. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Max Deutch, 634 N. Grand Blvd., St. Louis.
Secretary-Treasurer: Dr. Peter G. Danis, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society Bldg. Time: First Friday of each month from October to June.

Seattle Pediatric Society

President: Dr. Jay I. Durand, 1305–4th Ave., Seattle.
Secretary: Dr. Frederick B. Joy, 1215–4th Ave., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Secretary: Dr. Donald C. Shelby, 3780 Wilshire Blvd., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Campbell Harvey, 35 W. Huron St., Pontiac, Mich.
Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.
Time: Autumn, 1941.

Westchester County Medical Society, Pediatric Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.